THE GOULSTONIAN LECTURES

1900

DR. P. HORTON-SMITH

The Goulstonian Lectures

ON

THE TYPHOID BACILLUS

AND

TYPHOID FEVER

Delivered before the Royal College of Physicians of London on March 20th, 22nd, and 27th, 1900

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The Goulstonian Lectures

ON

THE TYPHOID BACILLUS AND TYPHOID FEVER.

LECTURE I.[1]

Mr. President and Gentlemen,—In the Goulstonian Lectures which he delivered nearly half a century ago the late Sir William Jenner expressed in appropriate language the feelings which should guide the lecturer in the choice of his subject. "It is fitting," he said, "that on this occasion the junior Fellow of the College should treat only of matters concerning which he has reason to hope his knowledge is inferior to that of his hearers in a less degree than on any other." In taking typhoid fever for my subject I trust that I may be fulfilling these conditions. I propose to discuss the pathology of the disease from its bacteriological aspect, for it is in this direction that recent researches have most materially extended our knowledge. To-day I desire, after considering some important points in connexion with the typhoid bacillus itself, to discuss the relationship which the latter bears to an ordinary case of typhoid fever.

Sir William Jenner[2] in his classical paper, published just 50 years ago, showed that in their clinical symptoms and in their morbid anatomy typhoid fever and typhus fever were separate diseases. A few months later, in a paper read before the Royal Medical and Chirurgical Society,[3] he supported his former thesis by proving, so far as inductive reasoning could prove the point, that the specific causes of the diseases were distinct. What the nature of the cause might be he did not discuss. Indeed, the words which Dr. Peter Mere Latham[4] had written some years before still

[1] Delivered on March 20th.

[2] On Fevers, London, 1893, p. 3; Edinburgh Monthly Journal of the Medical Sciences, 1849–50.

[3] Ibid., p. 139; Transactions of the Royal Medical and Chirurgical Society, vol. xxxiii.

[4] An Account of the Disease Lately Prevalent at the General Penitentiary, London, 1825, p. 140.

fairly well expressed the difficulty felt by even the very ablest minds in forming any definite conception of the pathology of the infectious diseases. Speaking of the epidemic prevalent at the General Penitentiary in 1825 and speculating on its cause Dr. Latham was obliged to confess that "the present state of our knowledge does not enable us to ascertain what the essence of the disease was, and indeed the search after the essence of any disease beyond the point at which it begins to fall within the reach of the senses has seldom brought the pathologist to any more certain conclusion than this—namely, that it consists in a morbid disposition or action which is *sui generis*." In truth, no further advance was possible until Pasteur had opened up a new world for us by demonstrating the connexion of micro-organisms with disease.

As soon as this had been effected numerous observers turned their attention to typhoid fever, each eager to discover the micro-organism in question. This honour was, however, reserved for Eberth[5] of Zürich who in 1880 succeeded in demonstrating in sections the presence of the true typhoid bacillus in the spleen and mesenteric glands. After its discovery and when its cultural characteristics had been pointed out by Gaffky,[6] it seemed an easy matter to identify the microbe, one or two cultures alone being sufficient to make certain of its identity. In 1885, however, the bacillus coli communis was discovered by Escherich[7] and it rapidly became evident that much greater care would have to be exercised in isolating the real typhoid bacillus. Indeed, so great became the difficulty in distinguishing the typhoid bacillus from some varieties of bacillus coli that in 1890 Rodet and Roux, representing the Lyons school of bacteriology, firmly maintained the view that distinction between them was impossible; that is to say, that by no morphological, cultural, or other tests was it possible to certainly distinguish the typhoid bacillus from members of the coli group, and, in fact, that the typhoid bacillus was nothing more than bacillus coli endowed temporarily with the power of producing a specially virulent toxine and thereby causing the disease. This we now know to be incorrect. It is, without doubt, true that the typhoid bacillus is a member of the great coli family. It is, in fact, nothing more than the member of that family which by a process of evolution has acquired the most highly specialised properties at the expense of some of the more common qualities possessed by the humbler members of the group; but the view that the ordinary bacillus coli communis can be converted at any moment into the typhoid bacillus, or that the reverse can obtain, is not supported by any evidence whatever. The species, though having a common ancestor, are now absolutely distinct. But though

[5] Virchow's Archiv, Band lxxxi., 1880, and Band lxxxiii., 1881.
[6] Mittheilungen aus dem Kaiserlichen Gesundheitsamte, Band ii., 1884.
[7] Fortschritte der Medicin, 1885.

this is so, and though with care the typhoid bacillus can be accurately distinguished from the other members of the group, it is by no means a simple matter, and I propose to dwell for a short time on the methods which should be employed for making the diagnosis, more especially as no definite criteria have as yet been agreed upon by bacteriologists, and consequently much valuable work has been vitiated by insufficient testing of the isolated micro-organisms.

The Identification of the Typhoid Bacillus.

In the first place, it may be said that there is not the smallest difficulty in distinguishing the typhoid bacillus from what may be called the classical bacillus coli communis. They resemble each other superficially, but differ essentially in that the typhoid bacillus does not, for example, form gas bubbles in dextrose gelatine, does not clot milk, nor form indol. The two can therefore be readily distinguished. The difficulty, however, in diagnosing the typhoid bacillus arises from the fact that the classical or typical bacillus coli communis is by no means the sole representative of this great group. Indeed, we now have to recognise the fact that the term "bacillus coli" does not refer to a single bacillus but to a great group of microbes, some of which are identical with the classical bacillus coli while others very closely indeed resemble the typhoid bacillus. Innumerable intermediate forms also exist. The credit of first thoroughly bringing home this important point belongs to Dr. M. H. Gordon [8] of St. Bartholomew's Hospital who, in an admirable paper published in 1897, very clearly demonstrated its truth. Dr. Gordon obtained from various sources, such as stools, urine, sewage, milk, water, &c., over 100 micro-organisms which resembled the bacillus coli communis morphologically and in its growth on gelatine and agar. He then proceeded to investigate the attributes of each; for example, their power of producing gas and indol, their capacity for acidifying and coagulating milk, the number of their flagella, &c. In this way he was able to demonstrate clearly what had been foreshadowed by Lawes and Andrewes,[9] that the 100 or more microbes, apparently all similar, could really be divided into as many as 16 different and stable varieties, according as they had lost one or more of the properties characteristic of the typical bacillus coli communis. Large as the number may seem, it by no means includes all the varieties known; indeed, to it we must now add several which resemble the typhoid bacillus most closely—for example, Petruchsky's bacillus fæcalis alkaligenes; Gärtner's bacillus enteritidis, Nocard's bacillus psittacosis, Günther's bacillus der fleisch-

[8] Journal of Pathology and Bacteriology, 1897.
[9] London County Council Reports, 1894.

vergiftung, Basenau's bacillus morbificans bovis (sometimes grouped together as "the Gärtner group"), and many others, such as, for example, Houston's bacillus typhosus simulans, isolated from Thames mud. These micro-organisms are important in themselves and they derive additional interest from the fact that they are not isolated bacilli but are merely representatives of a large group, continually being added to, from which the typhoid bacillus has to be very carefully distinguished.

In making, then, the diagnosis between the typhoid bacillus and its allies, on what tests should we rely? It may be stated at once that since no test is absolutely specific, with the exception of the one introduced by Pfeiffer, which in England at least is not always easy to perform, reliance must be placed on a series of tests. Let us now consider the most important of these and how they should be applied.

Morphology and motility.—In the first place, it should be noticed that an examination of the micro-organisms under the microscope often gives valuable indications provided that a fresh gelatine culture be used (agar cultures being much less distinctive) and that the examination be made in a drop of broth. Under these circumstances the greater length of the typhoid bacilli, their greater motility, and especially the curious serpentine movement of the longer forms, should at once suggest this micro-organism. Unfortunately, however, it cannot do more, for Gärtner's bacillus, Günther's bacillus, and Nocard's bacillus psittacosis, unlike the commoner varieties of the coli group, *exactly* resemble the typhoid bacillus in these respects. Still, the tests are of value in suggesting the presence of the typhoid bacillus and in excluding many of the commoner varieties of bacillus coli.

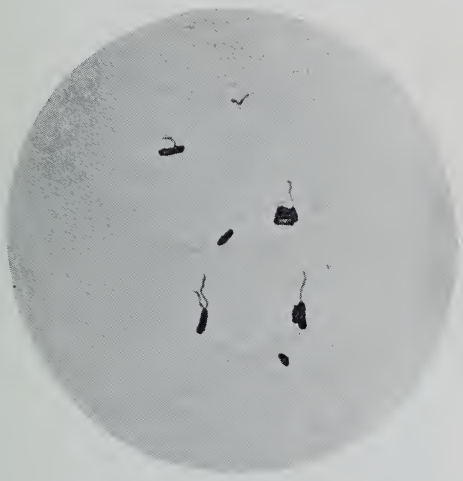
Recently, however, it has been shown that bacilli exactly resembling each other in appearance, size, and motility may yet differ radically in the shape and number of their flagella, and the point is of some importance in the diagnosis of the typhoid bacillus. Thus the flagella of this micro-organism are long and wavy and from eight to 12 in number on each bacillus, while those of the ordinary bacillus coli are shorter and vary in number from one to three. Until quite recently, therefore, it was thought that here bacteriologists possessed an infallible means of differentiating the two micro-organisms. But this is not so, for though the majority of the members of the coli group have but from one to three flagella, there are others which possess more, while one or two of the higher members of the group are multi-flagellated in exactly the same way as is the typhoid bacillus. These variations in the number of the flagella possessed by members of the coli family are well shown in the accompanying reproductions from photographs, for which I am indebted to the kindness of Dr. Gordon. We see from them that while very often

it is possible to distinguish the typhoid bacillus from its allies by the flagella test, yet sometimes this fails. Thus bacillus enteritidis, and probably also Nocard's bacillus, exactly resemble the typhoid bacillus, in this respect. As a rule, however, even in the multi-flagellated forms, slight differences can be made out and the test, therefore, is of very considerable importance. Thus the bacillus represented in photograph 1 was a variety of bacillus coli, which formed no gas, did not clot milk, and formed no indol, but the number and arrangement of its flagella at once enabled it to be distinguished from the typhoid bacillus. In all cases of doubt, therefore, the flagella should certainly be stained.

Photographs Showing the Variations in Flagella Possessed by Different Members of the Coli Family

(Prepared by Van Ermengem's Method by Dr. Gordon).

Fig. 1.

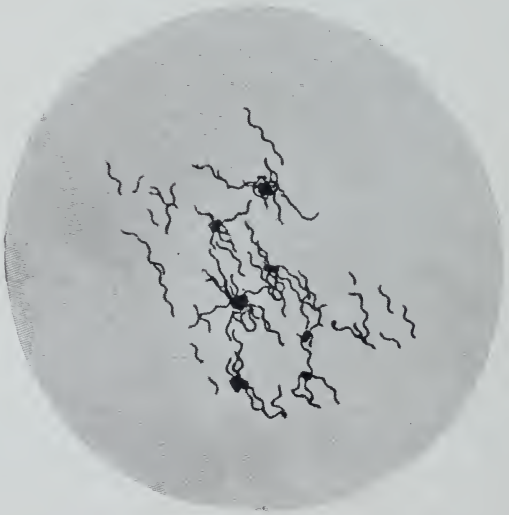


Bacillus Coli : variety (*a*), × 1000. This organism did not form gas or indol and did not clot milk.

FIG. 2.

Bacillus Coli : variety (*b*), × 1000. This organism formed both gas and indol and also clotted milk.

FIG. 3.



Bacillus Coli : variety (*c*), × 1000. This organism formed both gas and indol but did not clot milk.

FIG. 4.

Gärtner's Bacillus Enteritidis, × 1000.

FIG 5.

Bacillus Typhosus, × 1000.

Cultivation tests.—I do not propose to say anything about the growths of this great group of microbes on surface gelatine or agar, for the shades of differences noticed are too fine to be of any value as differential tests. Nor need I delay over the potato culture, hallowed though it be by tradition, owing to the fact that it was introduced by Gaffky himself, who first succeeded in cultivating the bacillus. The invisible growth, however, which may occur in the case of the typhoid bacillus if the reaction of the potato be suitable is not uncommonly also obtained with other members of the coli group, especially the higher members, and the test therefore becomes of but little use. So, too, with Elsner's medium, at first so much vaunted. According to my experience many varieties of bacillus coli grow on it exactly like the typhoid bacillus, and the medium, difficult at any time to prepare, becomes therefore of but little value.

Dextrose-agar and dextrose-gelatine.—Extremely important, however, as differential tests are the dextrose-agar and dextrose-gelatine shake cultures; probably, indeed, of all the culture tests they are the most important. Their value depends on the fact, first pointed out in 1890 by Theobald Smith,[10] that typhoid bacilli, grown in a medium containing 2 per cent. of dextrose, never decompose the latter with the formation of gas bubbles, while numerous members of the coli group do. Gordon, working with dextrose-gelatine, found that of his 16 varieties 11 produced the phenomenon, while the remaining five did not. Experience, however, shows that, contrary to the former tests, the chief members of the Gärtner group, otherwise closely allied to the typhoid bacillus, are sharply differentiated by this test. Thus of the four examples which I have been able to examine all gave a positive result. Petruchsky's bacillus fæcalis alkaligenes, however, is an exception; like the typhoid bacillus it forms no gas bubbles. As a rule, too, gas bubbles, if they are going to appear, generally are seen within 24 or 48 hours; occasionally, however, in dextrose-gelatine at least, they are delayed, it may be as long as for 10 days. If this medium be used it is well, therefore, to keep the tubes for a month before deciding that the reaction is really negative—the tests, then, are of the highest value, for though by no means conclusive in themselves, they yet often effect a distinction exactly in the cases where it is most required.

Litmus milk.—Another very important test is the litmus milk test. Originally introduced in 1891 by Chantemesse and Widal,[11] it was perfected in the following year by

[10] Centralblatt für Bakteriologie, 1890, vol. vii., p. 504.
[11] Société de Biologie, Paris, Nov. 7th, 1891, p. 747.

Dunbar,[12] who pointed out the importance of noticing the change of reaction as well as the presence or absence of coagulation. Grown in this medium and incubated at 37° C. the typhoid bacillus rapidly produces a slight acidity in the milk, but never, even after some months, does it coagulate the latter. With the typical bacillus coli communis, however, the reverse obtains, for the milk is clotted in from 24 to 48 hours, while the amount of acidity formed is greatly in excess of that ever produced by the typhoid bacillus. What, now, are the limitations of the test? 1. First, as regards the coagulation of the milk. Here, again, as with so many other tests, it is by no means infallible. Gordon found that 10 out of his 16 varieties of bacillus coli clotted while the other six failed to do so; moreover, of the four highly specialised members of the group which I have examined each had lost this power and so by this test could not be distinguished from the typhoid bacillus. A point of great importance to be borne in mind in conducting the test is that the coagulation of the milk in these cases is not uncommonly long delayed. As a rule it occurs within the first four days, but it is by no means rare with the less common varieties of bacillus coli to find it occurring first in the second, the third, or even the fourth week after inoculation of the tube. The lesson, therefore, to be drawn from this fact is that every tube should be observed for at least a month before stating that the result is negative. 2. Secondly, with regard to the production of acidity. This, I believe, is subject to less variation than the power of clotting milk, that is to say, that most varieties of bacillus coli form acid rapidly and form it more abundantly than does the typhoid bacillus. But, unfortunately, the test fails when we come to the more highly differentiated forms, for the Gärtner group all produce approximately the same amount of acid in milk as does the typhoid bacillus. So far I have spoken of the acidity, noticed up to the end of a week, the time usually allowed by observers before the tube is cast aside. If, however, the tubes be kept for a month before being discarded, as I have suggested, further important changes in the reaction may often be observed. Thus even at the end of this period the reaction of a typhoid milk culture is still nearly always acid. Such, at least, has been the case in the great majority of the different typhoid bacilli, over 20 in number, which I have examined. Occasionally, however, the reaction has been faintly alkaline. Supposing, however, we take the cultivations not of the typhoid bacillus but of the other highly specialised members of the coli group, bacillus enteritidis and its allies, we find that in certain of them, Gärtner's bacillus itself for example, at the end of a month the reaction is highly alkaline and has acquired a curious

[12] Zeitschrift für Hygiene, Band xii., 1892, p. 491.

but very definite slaty blue colour. Without going so far as to affirm that a typhoid bacillus could never give rise to such a change of reaction we may say at least that it can only rarely occur, and we should do well, therefore, to regard all such bacilli with grave suspicion until their identity with the typhoid bacillus has been otherwise most fully proved. We, may, then, affirm that the litmus milk test is of considerable value as a means of distinguishing the typhoid bacillus from the varieties of bacillus coli, if performed in the manner suggested, that is to say, if the culture is kept at 37° C. for at least one month. If discarded at the end of a week, as is the usual procedure, valuable indications are often lost.

Indol test.—Another test commonly applied to distinguish the typhoid bacillus is the indol test, introduced by Kitasato [13] in 1889. The bacilli are grown in broth at 37° C., and the cultures are tested at the end of a variable time, generally one week, to see whether indol is present in them or not. Typhoid bacilli under these conditions never form indol, various members of the coli group do. If the test is to be of any real value, however, it must not be performed before the end of one month, for in many cases the formation of the indol is much delayed. Even, however, if we take a month as the standard the test not uncommonly fails, and it should be noticed that this failure is especially common among the higher members of the group. Thus no indol was produced by any of the four members of the Gärtner group which I have examined, and the test, therefore, as a means of diagnosis becomes of infinitely less importance than the dextrose-agar or dextrose-gelatine test or the litmus milk test.

Media of Capaldi and Proskauer.—We now come to two tests for the typhoid bacillus which are too little known. I refer to the media introduced by Capaldi and Proskauer.[14] Into their composition I need not enter; suffice it to say that in Medium I. the bacillus coli grows readily and forms strong acidity, while the typhoid bacillus will not grow at all; in Medium II., on the contrary, while both grow readily the typhoid bacillus alone forms acid. The tests, like all the others which we have been discussing, have their limitations; but that they are of considerable value is shown by the fact that by means of them two of the four members of the Gärtner group which I have examined, as well as Houston's four bacilli (bacillus typhosus simulans, *a*, *b*, *c*, and *d*), were at once differentiated from the typhoid bacillus. In these media, then, we have a valuable auxiliary means of distinguishing the typhoid

[13] Ibid., Band vii., 1889, p. 515.
[14] Ibid., Band xxiii., p. 471.

bacillus from the other members of the coli group, rendered more important by the fact that the reaction is quickly given (in from 24 to 48 hours) and that the media can be easily prepared.[15]

Serum test.—We may now pass to the serum test, the most important of the tests which are commonly employed for the identification of the typhoid bacillus. This test, however, like all the others, only becomes of real diagnostic value if applied in the proper way. A not uncommon method of procedure is to take a broth culture of the suspected bacillus and to add to it sufficient serum from a patient suffering from typhoid fever to make a dilution of 1 in 20. Should clumping occur within an hour, or it may be two or even three hours, the bacillus is said to be the typhoid bacillus. Such a method of procedure, however, is really of no value, for we now know that in very many cases the serum of the typhoid fever patient is not a simple serum containing only the typhoid agglutinins but is a complex body containing the agglutinins of other microbes as well, and often those which we are most anxious to distinguish from the typhoid bacillus. Moreover, even if a simple typhoid serum is used—that is to say, a serum obtained from an animal immunised artificially by injections of typhoid culture, a fallacy may come in. Thus it is well known—it was, indeed, pointed out by Durham [16] in his earliest communication on the subject—that these sera are not "specific" but rather "specialised." The result is that if a very strongly agglutinating typhoid serum is used and a dilution of merely 1 in 20 be employed a bacillus, allied to the typhoid bacillus, but *not* the typhoid bacillus, may be clumped. Thus it was shown that Gärtner's bacillus may be agglutinated under these conditions, and other microbes of a similar kind also exist.

How, then, should the test be applied so as to guard against the possibility of such errors? In the first place, where possible a simple typhoid serum should be used for the test, that is to say one obtained from an animal highly immunised against the typhoid bacillus. Where, however, as is commonly the case, this is impossible, and a serum from a typhoid patient has to be employed, it should be one which agglutinates strongly, at least in dilutions of 1 in 1000, and the following method of procedure should be used. The serum should be tested against the standard typhoid bacillus (agar cultures in all cases being used) and the highest dilution in which a

[15] Medium I. is composed as follows: asparagin, 0·2; mannite, 0·2; sodium chloride, 0·02; magnesium sulphate, 0·01; calcium chloride, 0·02; mono-potassium phosphate, 0·2; and distilled water, 100. Medium II.: Witte's peptone, 2·0; mannite, 0·1; and distilled water, 100.

[16] Proceedings of the Royal Society, vol. lix., Jan. 3rd, 1896.

complete reaction is obtained in one hour should be worked out. When this is done then the unknown bacillus must be tested in like manner so that the maximum agglutinating power of the serum towards it may be also determined. If then the two prove equally sensitive towards the serum, each giving a complete reaction in one hour to a similar high dilution, then it may be said for certain, *provided it has answered the other tests*, that the unknown bacillus is also the typhoid bacillus; for experience shows that though a typhoid serum may agglutinate other microbes, for example, Gärtner's bacillus, as well as the typhoid bacillus, yet it probably never clumps the former in dilutions over 1 in 500 (Durham)[17] and indeed very rarely reaches such a height. If, then, the serum test, applied in this way, has given a positive reaction and the morphological and cultural tests are also affirmative, then we may be certain that the bacillus is also the typhoid bacillus.

Variations in clumping power according to the culture used; necessity of using cultures on solid media in testing typhoid bacilli.—Is, however, the converse true? Are we justified in saying that a bacillus which is only slightly sensitive to a strong typhoid serum is therefore not the typhoid bacillus, even though in all other respects it may resemble the latter? In other words, are all typhoid bacilli agglutinated by a given serum to an exactly equal extent? The majority of observers, Widal,[18] Bensaud,[19] Durham,[20] and others, have not noticed marked differences in this respect, and they believe, therefore, that typhoid bacilli from every source are agglutinated approximately to the same degree. Van de Velde,[21] however, from his observations on 20 different typhoid stocks found very considerable variations in the clumping power. The following observations are of interest in this connexion, for they show that using 18-hour broth cultures, as is now the usual practice, undoubtedly marked variations in the clumping power of different typhoid bacilli do exist. In these experiments typhoid sera of different typhoid clumping power were tested against the laboratory standard typhoid bacillus and also against typhoid bacilli isolated from stools, urine, mesenteric glands, and spleen—bacilli which, be it remembered, were found to resemble the typhoid bacillus in all respects both morphologically and culturally. As a result it was found that their clumping powers were by no means similar. Thus in Experiment 1 and Experiment 2 the bacilli isolated from the stools and urine of the same patient were agglutinated to a somewhat higher degree than was the standard bacillus. In Experiment 3, on the other

[17] The Lancet, Jan. 15th, 1898, p. 154.
[18] Annales de l'Institut Pasteur, 1897, p. 384.
[19] Thèse de Paris, 1897, p. 65.
[20] Journal of Pathology and Bacteriology, July, 1896.
[21] Bulletin de l'Académie de Belgique, 1897, ii., p. 261.

TABLE I.—VARIATIONS OF CLUMPING POWER MANIFESTED BY BROTH CULTURES OF DIFFERENT TYPHOID BACILLI.

—	Agglutinating strength of the given serum, as tested against a broth culture of the standard typhoid bacillus used in the laboratory for Widal examinations.	—	The same serum tested against the broth cultures of various other typhoid bacilli. Time limit in all cases one hour.
Experiment 1.—Serum (*a*) from a typhoid patient.	1.20 = + 1.200 = + 1.500 = + 1.1000 = + 1.2000 = trace.	Typhoid bacilli isolated from stools.	Col. I. 1.500 = + 1.1000 = + 1.2000 = just + Col. II. 1.500 = + 1.1000 = + 1.2000 = just + *Result.*—The bacilli clump a little more readily than the standard typhoid bacillus.
Experiment 2.—Serum (*b*) also from a typhoid patient.	1.200 = + 1.500 = partial. 1.1000 = 0	Typhoid bacilli isolated from urine.	Col. I. 1.200 = + 1.500 = just + 1.1000 = partial. Cols. II. and III. Gave a similar result. *Result.*—As in Experiment 1 the bacilli are rather more sensitive than the standard typhoid bacillus.
Experiment 3.—Serum (*c*) also from a typhoid patient.	1.20 = + 1.200 = + 1.1000 = partial. 1.2000 = trace.	Typhoid bacillus isolated from the spleen and mesenteric gland from a case fatal on the twenty-first day.	Spleen Col. I. 1.20 = + (just). 1.200 = trace. Mesenteric gland, Col. I. 1.20 = + (just). 1.200 = trace. *Result.*—The bacilli are far less sensitive than the standard typhoid bacillus.
Experiment 4.—(I.) Serum (*d*) from a patient inoculated against typhoid fever.	1.2000 = +	Typhoid bacillus isolated in pure culture from the spleen of an early fatal case.	1.20 = 0
(II.) The milk of a woman who had recently had typhoid fever.	1.20 = + 1.500 = + 1.1000 = +	"	1.20 = merest trace. 1.500 = 0 *Result.*—The isolated typhoid bacillus does not clump at all.
Experiment 5.—Serum (*e*) from a typhoid patient.	Standard bacillus I. 1.20 = + 1.50 = + 1.100 = partial. 1.200 = trace. 1.500 = 0	—	Standard bacillus II. 1.20 = + 1.50 = trace. 1.100 = 0 1.200 = 0 1.500 = 0 *Result.*—Standard bacillus I. is more sensitive than Standard bacillus II.

hand, the bacilli which had been obtained in pure culture from the spleen and mesenteric gland of a patient who died from typhoid fever on the twenty-first day were found to clump in a far less degree than the standard bacillus, while in Experiment 4 the bacillus, which had been isolated in pure culture from the spleen of a fatal case of typhoid fever was found to have no clumping power at all in a 1 in 20 dilution, though tested both against the highly agglutinating blood of a patient inoculated against typhoid fever and also against the milk of a patient who had recently had typhoid fever and in whom this secretion was strongly agglutinating. Experiment 5, also, is interesting. In this case two standard typhoid bacilli, both of which, that is to say, had been used in the routine work of the laboratory and which were very sensitive to typhoid serum, were tested against a feebly agglutinating serum, and the difference in their agglutinable power was distinct. The one clumped fairly in a 1 in 100 dilution, the other only in a dilution of 1 in 20. (See Table I.)

There can be no doubt, then, that if broth cultures be used typhoid bacilli often differ markedly among themselves in the ease with which they are affected by the typhoid agglutinins. But is this difference constant and have we here evidence of "varieties" of typhoid bacilli? It would seem not, for if we use cultures on solid media (agar and gelatine) this variability seems much less marked. This was especially noticeable in the case of the bacillus in Experiment 4, which, though it reacted like typhoid to all the morphological and culture tests enumerated above and had been obtained in pure culture from the spleen in an early fatal case, yet neither was agglutinated by typhoid serum when tested by Dr. Andrewes, nor by the typhoid milk when tested by myself. Feeling certain, however, that the bacillus *was* the typhoid bacillus I tried once more, but on this occasion used an agar culture (18 hours), testing it against a second sample of milk obtained from the same patient as before. A very different result was now obtained. After mixing the culture and the milk agglutination immediately became apparent in a dilution of 1 in 20, and in a few minutes was complete, while in a dilution of 1 in 500 a complete reaction was obtained within the hour—a result exactly similar to that given by the standard typhoid bacillus when tested against the sample of milk now under consideration.

This same extraordinary difference in sensibility to agglutination between broth and agar cultures I have noticed in the case of five other typhoid bacilli, isolated from different patients (and in a seventh case a similar result was obtained on using a gelatine culture), so that probably it is not really very uncommon. It is possible, too, that it should be associated with a fact observed by Kraus.[22] This experimenter showed that if broth cultures of the typhoid

[22] Wiener Klinische Wochenschrift, August 12th, 1897, No. 32.

bacillus be incubated for some days and be then filtered the filtrate gave rise on the addition of typhoid serum to a precipitate closely resembling in appearance that produced by agglutinated micro-organisms. The reaction was *specific* and only occurred when typhoid serum was added. It may be that the constituent of the bacillary body, on which the agglutinins act, and which thus seems normally to pass into the surrounding liquid, may in some cases diffuse much more easily, and even after 24 hours be no longer present in the bacilli themselves. We should thus have an easy explanation of the absence of the reaction in the broth-grown bacilli and its presence in those obtained from solid media. Be this as it may, the obvious moral to be drawn from the fact is that in testing the agglutinable qualities of a suspected bacillus cultures on solid media should always be used, and especially therefore agar cultures.

So far, too, though my experiments are not numerous enough for me to speak with certainty, I have not noticed more than slight differences between different typhoid bacilli, provided agar cultures be compared. The experiments of Dr. Klein,[23] however, showing that under abnormal conditions the agglutinable property of the cholera vibrio can be lost, should warn us not to be too dogmatic on this point in the case of the typhoid bacillus. Indeed, the matter requires further investigation.

Pfeiffer's test.—Should, however, a bacillus be discovered which culturally or morphologically resembles the typhoid bacillus in all respects and which yet agglutinates but feebly or not at all, then one further test must be applied to it—namely, Pfeiffer's test. This consists in injecting into the peritoneum of a guinea-pig a 10 times fatal dose of the bacillus in question, together with a very small quantity (0·001 cubic centimetre may be quite sufficient) of typhoid serum from a highly immunised animal. If the bacillus in question be the typhoid bacillus, then while a control animal injected *only* with the bacillus will die this animal will recover, the bacilli being converted first into granular masses (Pfeiffer's phenomenon) and then gradually disappearing under the influence of the lysogenic properties of the serum. Such a serum, however, is *specific*, and can therefore only protect, in minute doses, against the corresponding micro-organism. If, therefore, the bacillus in question be not the typhoid bacillus, but some variety of bacillus coli, the animal will infallibly die just like the control animal. This test is of the highest importance, for if properly performed a positive result i infallible. It is unfortunate, therefore, that the test, owing to the difficulties connected with it, cannot be made of more general application. It should, however, always be applied in any case in which there can be doubt as to the nature of the micro-

[23] Report of the Medical Officer of the Local Government Board, 1896-1897.

organism. If, for example, a bacillus which should fail to agglutinate nevertheless should react like the typhoid bacillus to this test, then we must accept it as the latter.

Such, then, are the most important methods which we possess for the identification of the typhoid bacillus. Without doubt by far the most important of these are the last two, the agglutination test carried out in high dilutions and Pfeiffer's test, but the others cannot be neglected. Indeed, in view of the extreme importance of the subject it would be well if before pronouncing any bacillus to be the typhoid bacillus, more especially if it be found in some unusual situation, whether within or without the body, the micro-organism were subjected, as a minimum, in all cases to the following tests which for convenience I here recapitulate: (1) morphology and motility (as observed on gelatine); (2) flagella; (3) gelatine and agar slope culture; (4) dextrose-agar or gelatine shake cultures, preferably the former; (5) litmus milk (one month); (6) broth culture (no indol—one month); (7) Proskauer and Capaldi medium 1 (no growth 48 hours); (8) Proskauer and Capaldi medium 2 (growth and acidity 48 hours); (9) agglutination test (high dilutions—1 in 1000 at least—agar cultures); and (10) in cases of doubt, Pfeiffer's test.

These tests are long and tedious, but it must be borne in mind that we know very few of the saprophytes with which we are surrounded and that at any moment one may be discovered having greater affinities with the typhoid bacillus than those already described. Remembering, too, the history of our subject it behoves us to use exceptional care, for only in this way can we hope that our results may withstand the just criticism of future observers.

The Typhoid Bacillus as a Saprophyte.

The life-history of the typhoid bacillus may be divided into two great chapters—the one dealing with the bacillus in its relation to the human body, the other describing its existence after leaving the shelter of the organism. It is to the former of these that I propose chiefly to confine myself, for our knowledge of the latter phase of the life-history of the micro-organism is as yet most limited. We are ignorant indeed whether under the conditions found in nature the bacillus can ever multiply and increase in numbers, or whether after a longer or shorter duration it gradually dies out.

The former view was recently brought forward by the late Sir Richard Thorne Thorne from a consideration of the fact that it was otherwise very difficult to explain the endemic character of typhoid fever in certain towns and districts. At the present time, however, the view is unsubstantiated by bacteriological evidence. It is true that, as Dr. Sidney Martin[24] has shown, the typhoid bacillus can multiply if

[24] Report of the Medical Officer of the Local Government Board, 1896-1897.

implanted in organically contaminated soil previously sterilised, but whether it would also multiply were the soil unsterilised and were it therefore exposed to the inevitable struggle for existence has not yet been shown. Indeed, the work of Lawes and Andrewes who showed that the typhoid bacillus rapidly died out if planted in sewage, whether sterilised or not, would rather suggest the improbability of its doing so.

Again, in support of the active saprophytic growth of the typhoid bacillus the very careful observations of Lösener[25] have been cited. In 1895 this observer, using all the means of differentiation then at his command, was able to find bacilli quite indistinguishable from the typhoid bacillus in very various situations, for instance, in the intestines of a pig, the water of his laboratory, and in a specimen of uncontaminated soil. Unfortunately, however, neither the serum nor Pfeiffer's test were then available, so that we are not justified in concluding that the bacilli in question really were the typhoid bacilli. On the contrary, the extraordinary difficulty experienced in finding the latter in water obviously specifically polluted would suggest that they were not.

We must allow, then, that so far there is no proof that the typhoid bacilli can multiply outside the human body. Our increasing knowledge of typhoid fever, too, enables us to explain satisfactorily many outbreaks of the disease without such an assumption. Thus it is fully established that a person may, though apparently restored to health, remain infectious for months and years after an attack of the fever—a fact in itself sufficient to account for many outbreaks of the disease. If, too, we remember that the bacillus has great power of resisting the effect of desiccation, remaining alive, it may be, for over a year in the dried condition (Schiller),[26] it becomes easy to understand how bacilli eliminated from the body may later pass into the atmosphere in the form of dust and cause disease at long periods after every fresh source of infection has been really removed. These facts should, in many cases at least, render unnecessary a belief in the actual growth of the bacillus outside the human body. The question, however, is one which the future alone can finally settle.

The Toxines of the Typhoid Bacillus.

The pathology and symptoms of any infectious diseases are intimately bound up with poisons elaborated by the microorganism in question. This subject was recently brought before the College by Dr. Sidney Martin in his Croonian Lectures, and I will not now do more than draw attention to two points in connexion with the toxines formed by the typhoid bacillus. The first point to note is that the poison is for the most part intracellular. It is contained in the

[25] Arbeiten aus dem Kaiserlichen Gesundheitsamte, ii., 1895, p. 207.
[26] Ibid., 1889, Band v., pp. 312 to 319.

bodies of the bacilli themselves and during their life passes only to a comparatively slight extent into the surrounding medium. Funck,[27] indeed, came to the conclusion that this never occurred, and this though he used both ordinary bacilli and also those whose virulence had been considerably heightened by successive passages through the guinea-pig. In both cases he found that if broth cultures were made and incubated at 37° C. for at least a month and then filtered through a Chamberland's bougie, the filtrate was innocuous. This, too, was my own experience, using a typhoid bacillus recently isolated and possessing moderate pathogenic power. Thus in the case of a rabbit whose initial weight was 1360 grammes I injected intravenously, in three successive doses, 18½ cubic centimetres of a filtered broth culture, the latter having been previously incubated at 37° C. for 42 days. This was followed 10 days later by a single subcutaneous injection of 18 cubic centimetres of the same filtered culture. A week later the animal was killed, four weeks from the initial injection. During the injections it had appeared in perfect health, its temperature had remained normal, and at its death it had gained 231 grammes. Post mortem, beyond slight parenchymatous changes in the liver and kidney nothing abnormal was observed. The poisonous characters of the filtered culture were therefore in this case almost *nil*.

There is no doubt, however, that in some cases the toxines do diffuse somewhat into the surrounding liquid. Thus Dr. Sidney Martin[28] was able on several occasions to produce lowered temperature, diarrhœa, and eventually death, by the injection of small doses (three cubic centimetres) of the filtered culture. But although this is so, and though there can be no doubt that sometimes to a slight extent the toxines do pass into the culture media, it remains true that the poisons are for the most part intracellular—a fact at once proved by noticing the incomparably greater effect produced on the animal by the injection of cultures in which the bacilli have been killed, but their bodies have been allowed to remain in the liquid. It may be accepted, then, that the toxines of the typhoid bacillus are for the most part contained within the bacillus itself and are chiefly set free when the latter is destroyed. The fact is of interest from a clinical point of view, for it shows that even when the body has acquired in a case of typhoid fever sufficient bacteriolytic power to destroy the bacilli we ought not to expect, in the absence of antitoxin formation, of which as yet there is no evidence, an immediate fall of temperature. The first effect, indeed, of the destruction of the bacilli would be a further outflow of poison into the general circulation, and only as this is gradually excreted should we expect the temperature to fall. In this way an explanation offers itself of the fall by lysis which is so characteristic of the disease.

The second point which it is of interest to note is that the

[27] La Sérothérapie de la Fièvre Typhoide, Bruxelles, 1896, pp. 34 to 38.
[28] Croonian Lectures, Brit. Med. Jour., vol. ii., 1898, pp. 11 and 73.

toxine is a very feeble one as compared with those of certain other micro-organisms. Thus, in order to kill a guinea-pig of 300 grammes weight Sanarelli[29] had to use a subcutaneous injection of 4·5 cubic centimetres of his toxine, while in the case of tetanus Vaillard was able to obtain a solution $\frac{1}{5000000}$ cubic centimetre of which was able to kill a guinea-pig. In the case of diphtheria, too, the dose necessary may be extremely small. It is obvious, then, that to explain the symptoms of typhoid fever the number of bacilli present in the body should be very large, so that sufficient toxine may be formed. As we shall see, this is what does occur. So far from being limited to one situation, as in tetanus, the bacilli find their habitat in many organs and in diverse situations of the body and are present in enormous numbers.

Experimental Typhoid Fever.

Before a given micro-organism can be accepted as the cause of a disease two points must be clearly established. In the first place the organism must be constantly present in the tissues of patients suffering from the disease, and secondly, the bacillus, having been obtained in pure culture and grown artificially through several generations, must be able to reproduce the disease.

With regard to typhoid fever there can be no doubt about the former of the two premisses. The bacillus is present in the body in all cases of the disease. Indeed, this is so well recognised abroad that puncture of the spleen with the object of isolating the bacillus is one of the recognised means of clinical diagnosis practised by the continental physician. Is, however, the second premiss true. Can the bacillus when reintroduced again give rise to the disease? For a long time this was doubted, innumerable attempts to reproduce the disease in animals, both by feeding and by inoculation, having resulted in failure. Animals, in fact, as a rule are not susceptible to typhoid fever such as it occurs in man. The observations of Mr. Bland Sutton,[30] however, on the animals (lemurs, monkeys, beavers, &c.) in the Zoological Gardens seemed to show that, under certain conditions at least, the lower animals could suffer from true typhoid fever. At all events, the clinical symptoms in these animals, fever, in some cases of six weeks' duration, and diarrhœa, the ulceration of the Peyer's patches and solitary follicles found post mortem, and the mode of death, brought about in one case at least by general peritonitis and in another by sudden hæmorrhage from the bowel, gave a picture quite indistinguishable from the disease occurring in man. Moreover, this disease was raging in the neighbourhood at the time. It was reasonable, therefore, to hope that further persistent effort might eventually result in

[29] Annales de l'Institut Pasteur, 1894, p. 199.
[30] Transactions of the Pathological Society of London, 1885.

producing by means of the typhoid bacillus typical typhoid fever, and it would seem that Remlinger has lately succeeded where so many others have failed. His experiments, it should be noticed, were carried on during the summer in Tunis, and it is conceivable that the tropical climate may by its effect on the animals have had something to do with the successful result. Remlinger [31] experimented first on rabbits. His method consisted in feeding them on vegetables previously soaked in water largely diluted with typhoid cultures. Under this treatment and after a short incubation period three of the eight rabbits used became ill. The temperature rose gradually and remained raised; the animals were affected with diarrhœa and they refused food and rapidly lost weight. The temperature charts strongly resembled in appearance those of typhoid fever, the temperature remaining up for from 12 to 16 days. In two cases death followed and in one recovery. In all three cases Widal's reaction, 1 in 50, was obtained from the blood during life. In the two cases which died the post-mortem appearances obtained were those of typhoid fever. The ileum was found to be much injected, the Peyer's patches were swollen and hypertrophied, and near the cæcum there was some ulceration. The mesenteric glands were swollen, the spleen was enlarged, and in one case diffluent. In both cases typhoid bacilli were isolated from the latter organ. With white rats, also, a very similar result was obtained. It would seem, then, that there cannot be any further doubt that typhoid fever can be communicated to animals by means of the typhoid bacillus. The last link, therefore, in the chain of evidence proving the causal connexion of the bacillus with the disease may be regarded as complete.

Human Typhoid Fever; the Distribution of the Bacillus in the Body.

I may now pass from the disease experimentally induced in animals to typhoid fever as it occurs in man, and I propose first of all to discuss the relationship which the bacillus bears to an ordinary case of the disease. This may be best effected by considering in such a case what are the situations of the body in which the bacillus may be found.

Mesenteric glands and spleen.—Eberth,[32] the discoverer of the bacillus, was able to demonstrate its presence microscopically in the mesenteric glands and in the spleen. He did not, indeed, find the bacillus in all cases, but he was successful six times in the spleen and 12 times in the mesenteric glands out of 23 cases which he examined. Further investigation, however, not only confirmed his discovery but showed that the presence of the micro-organisms in these

[31] Annales de l'Institut Pasteur, 1897, p. 829.
[32] Loc. cit., vide note 5.

situations was constant. In rare cases, it is true, a culture from either organ may remain sterile, but this doubtless arises from the curious manner in which the bacilli are scattered in little masses through the tissue so that occasionally the inoculating needle fails to come in contact with them.

Peyer's patches.—With regard also to the Peyer's patches themselves and the solitary follicles of the intestine there is no doubt that, if examined early enough, typhoid bacilli may be demonstrated therein.

The liver.—Another organ in which the typhoid bacillus is constantly present is the liver. Thus Gaffky found it here in 12 out of his 13 examinations, and his results have been fully confirmed. In the liver again, just as in the Peyer's patches, the mesenteric glands, and the spleen, the typhoid bacilli are found aggregated together into their little characteristic masses. It might at first seem somewhat surprising that the liver should contain the typhoid bacillus, but it is not difficult to explain. As we shall see, the bacilli must in all cases at some period of the disease pass into the blood and hence be first carried to the liver. Now this organ, as Lemaire [33] has clearly shown, undoubtedly plays a very active part in eliminating the typhoid bacillus from the circulation, even more so than the spleen. For both reasons, therefore, it is easy to understand how the liver comes to be a constant habitat of the bacillus in typhoid fever.

The bile.—This, however, has been known for long. Much more recent is the knowledge that the bile in the gall-bladder in the majority of cases contains the bacillus, very often in pure culture. For this advance in our knowledge we are especially indebted to Chiari [34] who in 1893 examined the bile in 22 cases of typhoid fever, and in 19 of them found the typhoid bacillus therein. Moreover, in 15 of these it was present in pure culture. Somewhat similar results had, indeed, been obtained before experimentally. Thus Blachstein and Welch [35] in 1891 showed that if mild doses of typhoid culture were injected intravenously into rabbits, on examination after death the bile would often present a pure culture of the typhoid bacillus. To Chiari, however, belongs the credit of demonstrating the fact in cases of typhoid fever in man and his observations have been fully confirmed. Thus in 10 cases at St. Bartholomew's Hospital in which the bile was examined, in nine of them was the bacillus found; in each case also it was in pure culture. Flexner [36] was, however, less fortunate, finding them only in seven out of 14 examinations. It should be noticed, also, that in

[33] Archives de Médecine Expérimentale, Septembre, 1899.
[34] Zeitschrift für Heilkunde, xv., 1894. p. 199.
[35] Bulletin of the Johns Hopkins Hospital, 1891, pp. 96 and 121
[36] Quoted by Osler; Transactions of the Association of American Physicians, vol. xii., p. 385.

very many cases the micro-organisms are present in great numbers, so that if a drop of bile be examined under a microscope numerous bacilli may be seen.

The bone marrow.—Another situation, also, in which the bacilli have been recently demonstrated with great frequency is the bone marrow. This was shown as recently as 1894 by Quincke.[37] He examined the marrow of the ribs in nine cases and in eight of them he found the typhoid bacillus in considerable numbers. In seven the bacilli were present in pure culture. His method of diagnosing the bacilli, it is true, left much to be desired; still there is no doubt from the confirmation which his observations have received that the bacilli found by him were really true typhoid bacilli. At St. Bartholomew's Hospital the bone marrow has been examined in six cases and in four of them a pure culture of typhoid bacilli was obtained. In the other two cases typhoid bacilli were not found, but only bacillus proteus vulgaris and bacillus coli.

The kidney.—We may now pass to another organ which contains sometimes the specific micro-organism—namely, the kidney. As a matter of fact, however, in contradistinction to what we have seen to be true for the liver, the spleen, and the mesenteric glands, the bacillus is by no means constantly found here. Its presence, indeed, is exceptional. Thus, to mention only recent observations, Flexner[38] found it here in one case out of four, in addition to two cases of obvious typhoid septicæmia in which the bacilli were found in the blood and all the organs after death. Wright and Stokes[39] found it in three cases out of seven. For myself I may say that I have examined the kidneys bacteriologically on eight occasions. Twice only were the typhoid bacilli found, and in both of these the micro-organism was present in large quantities also in the blood. In the remaining cases the kidneys were sterile three times, and on three occasions they contained bacillus coli communis, twice in pure culture and once combined with bacillus proteus vulgaris. We shall probably, therefore, be not far wrong if we conclude that it is the exception rather than the rule for typhoid bacilli to be found in the kidney after death, though in rare cases, as I shall show, it may become localised here and give rise to an acute nephritis. Although, however, this is so, it is probable that during life it is by no means uncommon for typhoid bacilli to be carried every now and then in small numbers to the kidney and then to be rapidly excreted into the urine, for how else are we to explain the frequent occurrence of the bacilli in this excretion?

The lung.—In other organs, too, the typhoid bacillus has been described not infrequently, for example, in the lung.

[37] Berliner Klinische Wochenschrift, 1894, p. 351.
[38] Johns Hopkins Hospital Reports, 1895, vol. v.
[39] Boston Medical and Surgical Journal, April, 1895, p. 333.

Here the bacillus does undoubtedly occur, but not, I believe, as frequently as is sometimes imagined. Thus, in five cases in which I have examined the lung, in one only has the typhoid bacillus been present, this being a case of thrombosis of the pulmonary artery and infarction of the lung. In four others (two examples of lobar pneumonia, one of hypostatic pneumonia, and one of simple congestion), the typhoid bacilli were not found, though in two cases the bacillus coli was present in considerable numbers. The late Professor Kanthack also had a similar experience, since in four cases of broncho-pneumonia he was never once able to discover the specific organisms, though bacillus coli was present on more than one occasion.

In less suspected regions, too, as, for example, the testicle, the typhoid bacillus may be present even in the absence of any definite complication.

It will be seen, then, from what has been said that the bacilli are found in uncomplicated cases of typhoid fever with great constancy in the Peyer's patches, in the solitary follicles, in the mesenteric glands, in the spleen, and with great frequency in the red marrow of the bones and in the bile, not uncommonly in the kidney, and sometimes in the lung. In other organs, too, such, for example, as the testicle, their presence has been discovered. The relative frequency of their occurrence in these situations is shown in the following table from the St. Bartholomew's Hospital post-mortem records, the observations having been made by the late Professor Kanthack, by Dr. Andrewes, and by myself.

TABLE II.—*Showing the Relative Frequency of Occurrence of the Typhoid Bacillus in the Various Organs of the Body.*

—	Number of times examined.	Typhoid bacilli found.
Spleen	21	20
Mesenteric gland...	13	12
Liver	4	3
Bile	10	9
Bone marrow	6	4
Kidney	8	2
Blood from the heart...	10	2
Lung	9	1
Thyroid	1	0

It is evident, from a consideration of this table, that the bacilli are always widely distributed in the body and there would seem to be only one means by which such a wide distribution could be effected, and that is through the blood. Are, however, the bacilli found in the blood?

The Blood.

In answering this question it will be well to consider first of all the results which have been obtained from an examination of the blood in fatal cases. In such cases, though it is not by any means the rule to find the typhoid bacillus in the blood after death, yet it occurs there by no means infrequently. Thus Vincent[40] found the bacillus in one case out of four and Flexner[41] in two cases out of six. Klein[42] recorded their presence in two out of four cases, a similar result also being obtained by Wright and Stokes. Lately I have examined the blood after death on nine occasions, and three other cases are recorded in our records at St. Bartholomew's Hospital. Of these 12 cases two gave a positive result, the typhoid bacilli being demonstrated in the blood with ease. Of the remaining 10 cases, five were sterile, three contained bacillus coli and bacillus proteus vulgaris, and two the pyogenic cocci. Table III. shows these results more exactly.

Table III.—*Showing the results of Post-mortem Examination of the Blood in Fatal Cases of Typhoid Fever.*

Total number of cases examined, 12.

Sterile	5	Streptococci and staphylococci	1
Typhoid bacilli	2	Bacillus coli	2
Streptococci	1	Bacillus coli and proteus	1

It is interesting to note in passing that one of the cases in which the typhoid bacilli were found in the blood was that of a girl who died on the fourteenth day from the "severity of the disease" and "heart failure." It is possible that not a few of the cases which die thus early may really prove to be cases of similar marked typhoid septicæmia.

It will be seen, then, that out of a total of 30 cases in which the blood was examined after death the typhoid bacillus was found in nine of them. Evidently, then, in *fatal* cases it is not uncommon for the typhoid bacilli to be present in the blood in considerable numbers. But does the same occur in *non-fatal* cases during life, and is it easy to demonstrate the presence of the bacilli in the circulating blood? It may be said at once that it is a matter of extreme difficulty; indeed, it was held until quite recently to be almost impossible. Seitz[43] failed in seven cases, Janowski[44] in 27, Lucatello[45] in nine, Klein[46] in 10, and Fraenkel and Simmonds[47] in six. Occasionally, however,

[40] Annales de l'Institut Pasteur, 1893.
[41] Loc. cit., vide note 38.
[42] Report of the Medical Officer of the Local Government Board, 1892-93
[43] Jahresbericht über Pathologische Micro-organismen, 1886, p. 165.
[44] Centralblatt für Bakteriologie, 1889, p. 657.
[45] Jahresbericht über Pathologische Micro-organismen, 1886, p. 176.
[46] Loc. cit., vide note 42.
[47] Centralblatt für Klinische Medicin, 1885, p. 737.

a positive result has been recorded; thus Thiemich[48] was once successful out of seven cases, Wiltschur (quoted by Janowski) once in 31, and Ettlinger twice out of 10 cases. Lastly, Stern[49] recently reports two successes and Block[50] one. In all seven successful cases are here mentioned against 110 failures. As a matter of fact, however, these results are misleading, for Kühnau[51] has lately shown that if much larger quantities of blood be taken than was used by the earlier observers — five to ten cubic centimetres, for example — and especially if the blood be immediately diluted after it has been obtained, to diminish its bactericidal power, then it is possible to obtain the bacillus from the blood during life in a very considerable percentage of cases. Working on these lines Kühnau was successful in 11 out of 41 cases. It should be noticed, however, that the number of colonies which developed were always extremely small, the total number varying from two to nine. If, then, when we examine only 10 cubic centimetres of blood we are able to demonstrate the bacillus in 25 per cent. of cases of typhoid fever, it is no rash assumption to believe that, were we able to examine the whole, we should always find it in the circulating blood during life. The reason why the bacilli are not found in greater numbers in the blood during life probably depends on the fact that in ordinary cases the blood is an extremely bad medium for their growth. Indeed, owing to its bactericidal power it is likely that such bacilli as do not succeed in finding shelter in some viscus are rapidly destroyed. This would not occur to the same extent in fatal cases (perforation and similar cases being excluded), for often it is owing to such patients acquiring this power that a fatal termination ensues, and on this fact doubtless in part depends the greater ease with which the bacilli can be demonstrated in the blood after death. We may believe, therefore, as indeed we should expect from the distribution of the bacillus in the body, that the micro-organisms pass into the blood in all cases of typhoid fever. They are, however, rapidly eliminated from it into the various organs or destroyed. In rarer cases, on the contrary, probably always fatal, when the blood fails to acquire bactericidal properties, the typhoid bacilli may develop therein and be found after death in considerable numbers.

The Typhoid Eruption.

The general distribution of the typhoid bacillus in the organs of a patient suffering from typhoid fever has now been considered, and it is obvious from the facts brought forward that typhoid fever is far from being merely an

[48] Jahresbericht über Pathologische Micro-organismen, 1894, p. 266.
[49] Centralblatt für Innere Medicin, 1896, p. 1249.
[50] Bulletin of the Johns Hopkins Hospital, 1897, p. 119.
[51] Zeitschrift für Hygiene, vol. xxv., 1897.

intestinal disease. Bearing this in mind it will be interesting to consider the relation of the bacilli to the "spots"—the roseolous eruption characteristic of the illness.

The early observers for the most part were unable to demonstrate the presence of the bacilli in this lesion. Thus Wiltschur,[52] Seitz,[53] Curschmann,[54] Merkel and Goldschmidt,[55] and others in their numerous experiments all obtained negative results, while Rutimeyer[56] obtained one positive result in six observations. In the light of these results the statement of Neuhaus,[57] made as long ago as 1886, that he had obtained nine positive results in 15 cases, was generally received with incredulity. It may be said, therefore, that until quite recently the received opinion was that the spots in typhoid fever were not due to a local growth of the typhoid bacilli, but were more probably due to the absorption of the typhoid toxines into the general circulation.

Observers, however, were not entirely satisfied and continued working at the subject. In 1895 Thiemich[58] reported that he had found the bacilli in the spots in three cases out of seven, while early in 1899 appeared the important paper by Neufeld,[59] which apparently explained the discrepancies between the results of various observers. Neufeld argued that if the bacilli really were the cause, it was evident they were only able to obtain their foothold in the skin and subcutaneous tissue for a very short time, otherwise the spots themselves would not be so fleeing—hence to find them spots should be examined quite early in their development. Secondly, to eliminate as far as possible the bactericidal power of the blood itself, which would come in contact with the bacilli as soon as the spot was opened, he advocated the use of liquid culture media (broth) in order to dilute the blood and so diminish this source of error. The value of these suggestions was shown by his results. He examined the spots in 14 cases and in 13 he obtained a positive result. His methods of testing the bacilli obtained were, it may be stated, admirable. These results were confirmed in November of last year by Curschmann[60] of Leipzig. Following Neufeld's methods he examined the spots in 20 cases and in 14 he was able to demonstrate the typhoid bacilli, certain of his negative results also being evidently due to his having in some cases chosen spots already beginning to fade. Lastly, within the last few weeks, Richardson[61] of Boston, an extremely careful observer, reports similar successful results, the bacilli being isolated from the spots on an average six days *before* the Widal

[52] Quoted by Janowski. Loc. cit., vide note 44.
[53] Loc. cit., vide note 43.
[54] Der Unterleibstyphus, Wien, 1898.
[55] Centralblatt für Klinische Medicin, 1887, p. 392.
[56] Ibid., p. 145.
[57] Berliner Klinische Wochenschrift, No. 6 and No. 24, 1886.
[58] Deutsche Medicinische Wochenschrift, 1895, No. 34, p. 550.
[59] Zeitschrift für Hygiene, 1899, Band xxx., p. 498.
[60] Münchener Medicinische Wochenschrift, Nov. 28th, 1899.
[61] Journal of the Boston Society of the Medical Sciences, Jan. 16th, 1900, p. 110.

reaction was obtained. It should be added, however, that the number of typhoid bacilli in each individual spot must be very small, for though many observers have endeavoured to demonstrate them microscopically therein, they have never yet succeeded (Ernst[62] and Neufeld[63]). There would seem, then, to be hardly any doubt whatever that the rose spots are truly specific in nature and are the result of the direct presence of the typhoid bacillus.

The Excretions.

Having now discussed the usual distribution of the specific microbe in the various organs in an uncomplicated case of typhoid fever we may turn our attention to the excretions, for it is of great importance to know how far each of these is infectious. There are four which have been so described with more or less frequency—the sweat, the expectoration, the fæces, and the urine.

The sweat.—With regard first of all to the sweat. There would seem to be *a priori* no reason why typhoid bacilli should not be found therein, since there is no doubt that the bacillus always passes into the blood. At present, however, there is really no evidence to show that they do occur in this excretion. Three positive observations have, it is true, been recorded in addition to numerous negative ones, but the observers, Geisler[64] and Sudakoff,[65] seem to have taken no special care to prove the identity of the micro-organism found, and for the present, therefore, their results may be disregarded.

The expectoration.—With regard to the expectoration the case is somewhat different. I have shown that the typhoid bacillus may be present in the lung in large numbers, and whenever this occurs we must believe that the sputum will always contain the micro-organism. Fortunately, however, these cases are rare, but nevertheless we should always look upon the expectoration in a case of typhoid fever, if there be any, as a possible means of spreading the disease and should take measures accordingly.

The fæces.—The idea that the fæces were the chief means whereby the disease was conveyed seems to have been first explicitly stated by Canstatt in 1847, and in this country Dr. William Budd long and ably maintained this view.[66] Indeed, it is probably due to his enthusiastic teaching that the doctrine of the intensely contagious character of typhoid stools throughout the whole course of the disease has held

[62] Ziegler: Beiträge zur Pathologischen Anatomie, viii., 1890, p. 195.
[63] Loc. cit, vide note 59.
[64] Centralblatt für Bakteriologie, vol. xiii., 1893, p. 767.
[65] Ibid., vol. xxv., 1899, p. 575.
[66] For an interesting, if somewhat highly-coloured, description of the dangers resulting from the stools reference should be made to Dr. Budd's work on "Typhoid Fever," London, 1873, p. 52.

its ground ever since. Lately, however, a distinction has been drawn between the alvine dejections and the urine, and though it is absolutely certain that excremental pollution in its broad sense is the great cause of the spread of typhoid fever, it is at the present moment still debated how great is the share taken by the fæces and the urine respectively, and at what period of the disease each should be regarded as most dangerous. In the early days of bacteriology no difficulty was experienced in isolating the typhoid bacilli from the stools. It was open to anyone to effect this. The rapid progress of knowledge, however, soon showed that these were not typhoid bacilli, but merely bacillus coli communis or one of its numerous varieties, and it was then recognised that so far from being easy it was a matter of most extraordinary difficulty to find the true bacilli in the fæces. Thus Walthelet [67] in 1895 could only isolate the micro-organism in four stools, though he examined as many as 51. In 1896, however, the introduction of Elsner's medium somewhat facilitated matters and led at all events to renewed investigations. As a result we may say that there can be now no reasonable doubt that in the first and second weeks of typhoid fever the stools are highly infectious. The numerous observations of Pollak,[68] Jemma,[69] and Richardson [70] show that the typhoid bacilli can be found in them in practically every case at this period of the disease. An extremely important point, it may be remarked in passing, for it completely annihilates the fanciful but well-known theory of Sanarelli that typhoid fever is primarily a septicæmia and that the intestinal lesions are merely secondary. At later periods of the disease, however, and also during convalescence, if care be taken to obtain fæces uncontaminated with urine, it is extremely difficult to isolate the micro-organism. Thus Jemma,[71] Richardson,[72] and Lazarus [73] all found great difficulty at this stage, and my own observations bear out their results. Thus out of 20 observations (Table IV.) made during the later periods of the disease, sloughs being actually present in the stools in some instances, in one only was a positive result obtained, and in this case a relapse very shortly followed; though in the three cases in which the examinations were made before the seventeenth day in each the typhoid bacilli were demonstrated at the second attempt.

It would be wrong, of course, to assume that because the micro-organisms cannot be demonstrated by our imperfect technique after the beginning of the third week that therefore they are not present. We have seen, indeed, that the gall-bladder may contain a pure culture of typhoid bacilli at

[67] Annales de l'Institut Pasteur, 1895, p. 252.
[68] Centralblatt für Innere Medicin, 1896, p. 785.
[69] Münchener Medicinische Wochenschrift, 1897, No. 33.
[70] Boston Medical and Surgical Journal, 1897, p. 443; Brit. Med. Jour., Dec. 25th, 1897.
[71] Loc. cit., vide note 69. [72] Loc. cit., vide note 70.
[73] Berliner Klinische Wochenschrift, Dec. 9th, 1895, p. 1068.

TABLE IV.—*Observations made on Typhoid Stools (obtained separate from urine) for the most part in the Later Stages of the Disease.*

No.	Age and sex.	Day of disease.	Character of stool.	Result.*
1	24, F.	8th } attack	Semi-solid	—
		11th } attack	,,	+
		15th } attack	,,	—
		Convalescent, 20 days	Solid	—
2	16, M.	13th } attack	Semi-solid	—
		17th } attack	Solid	+
		25th } attack	,,	—
		32nd } attack	Semi-solid	—
		T. N., 5 days	Solid	—
		? 1st day of a relapse	,,	—
		Convalescent, 6 days	Semi-solid	—
3	22, M.	9th } attack	Peasoupy	—
		14th } attack	,,	+
		18th } attack	—	—
		21st } attack	Semi-solid	—
		T. N., 4 days	,,	+
		1st day of relapse	Solid	—
		5th ,, ,,	,,	—
		9th ,, ,,	,,	—
		Convalescent, 3 days	,,	—
		Convalescent, 10 days	,,	—
4	9, M.	19th day } attack	Peasoupy	—
		25th day } attack	,,	—
		Convalescent, 13 days	Formed	—
5	42, M.	2 days before end of long relapse	Semi-solid	—
		Convalescent, 11 days	Solid	—
6	18, M.	Convalescent, 4 days	Semi-solid	—
7	21, M.	28th day	,,	—

* + signifies a positive result, typhoid bacilli being found in the stools. − signifies a negative result, typhoid bacilli not being found. T. N. = Temperature normal.

For further details consult THE LANCET, May 20th, 1899, p. 1346.

the patient's death late on in the disease, and as a matter of fact this condition may continue for weeks, months, and even years after the primary attack. Whilst this lasts we must assume that the specific germ is carried with the bile into the alimentary canal, and we might therefore expect to find it in the fæces. It is possible, however, that if present only in small numbers the typhoid bacilli may be rapidly destroyed as soon as they come in contact with the other micro-organisms in the alimentary canal, for the toxines of not a few of them are extremely inimical towards the typhoid bacillus. This, however, though possible, has not yet been actually proved, and at present the following are the facts of which we are in actual possession. The specific micro-organism can be demonstrated in the stools if care be taken during the first and second and early part of the third week of the disease and possibly during the early part of the relapse. Later it cannot be demonstrated by our present methods. It follows, therefore, that the fæces are highly infectious at the commencement of the disease and that later they become much less dangerous. How soon they become absolutely innocuous cannot be stated, but we must be prepared for the possibility of their remaining in some cases a source of danger for long periods after the patient is apparently well—as long, that is to say, as the bile continues to harbour the parasite. It is quite possible, indeed, that certain epidemics in which the sanitary conditions were at fault and in which no obvious case of typhoid fever had been previously imported may have been caused by cases of this kind—epidemics which must always have a high interest for us, since it was from a consideration of them that Murchison was led to formulate his belief that in some cases at least typhoid fever could originate *de novo* and which prompted him therefore to name the disease "pythogenic fever."

The urine.—Passing now from the stools to the urine, the other great secretion by means of which typhoid fever is spread—or, as I believe myself, the chief means—I will only say now that, unlike the fæces, the urine only becomes dangerous in one out of every four cases of the disease and that as a rule it is towards the end of the disease or during convalescence that this condition occurs. In one other point, too, we notice a contrast and that is that while it is always difficult to find the typhoid bacilli in the stools in the urine it is always easy, for when they occur they are nearly always in pure culture and not uncommonly they are present in such extraordinary numbers that one cubic centimetre may contain as many as 500,000,000 micro-organisms. The danger of such a "constant supply" needs no comment, though incidentally it shows that our means of protection against the invasion of the typhoid bacillus are much greater than is generally supposed.

Conclusion.

If, now, we consider the facts which have been brought forward in connexion with the bacteriology of an ordinary case of typhoid fever we obtain the following data. The typhoid bacillus can always be found in the stools in the early periods of the disease. It can also be demonstrated always in the Peyer's patches and the mesenteric glands. It does not, however, remain limited to these situations but very soon and in all cases passes into the blood (from which it can be very often isolated) and by means of which it is distributed to the most diverse organs. Thus it can be always found in the spleen and in the liver. It gives rise in the skin to the typical eruption. It is in most cases present in the marrow of the bone and in the bile. It is frequently present in the urine, and is not uncommonly found in the kidneys. Occasionally, also, it may be detected in the lungs and sometimes in other organs.

And now we may ask, How do these facts bear upon our conception of typhoid fever? The answer is clear. Any conception of the disease which regards it merely as affecting the alimentary canal only can no longer be maintained. On the contrary, so far from considering it as an intestinal disease pure and simple, we should rather look upon it as a *modified form of septicæmia*. It is septicæmia in that always and in all cases the bacilli pass into the blood and then into the various organs, and in that the symptoms, excepting as far as they are intestinal, are referable to the poisons there produced. It is a modified form, however, in that in nearly all cases there is a definite local and primary disease whence the secondary dissemination of the micro-organism takes place.

Looked at in this way we have a ready explanation of the fact that the severity of the disease bears no relation to the number and character of the intestinal lesions. For just as a fatal septicæmia may originate in a scratch, so one or two small typhoid ulcers may be quite sufficient to allow the entry of the micro-organism and the development of the disease.

LECTURE II.[1]

Mr. President and Gentlemen,—In my first lecture I discussed the bacteriology of an ordinary case of typhoid fever. To-day I desire to consider abnormal varieties of typhoid infection, and the relation which the bacillus bears to the chief complications and sequelæ of the disease. Before, however, passing to this subject it will be well to turn our attention for a short time to the question of relapses, for recent work enables us to offer at least a partial explanation of this interesting condition.

Relapses in Typhoid Fever.

In the first place it must be allowed that a relapse is nothing less than a complete renewal of the primary disease. As a rule the whole cycle of changes met with in the first attack is again passed through. Thus fresh intestinal lesions are produced and a second generalisation of the bacilli occurs, as evidenced by the recurrence of the typical eruption. Indeed, the only difference which can be noticed between the attack and the relapse is that, as a rule, the duration of the latter is somewhat less than that of the former, though even in this respect exceptions are by no means uncommon. How, then, are we to explain this complete re-infection, at a time, too, when the protection acquired by the former attack has already begun to manifest itself? The experiments of Chantemesse and Widal and of Sanarelli throw light on the matter.

It is well known that the typhoid bacillus, whether isolated from the tissues after death or obtained from the stools or urine during life, has, for animals at least, but a low degree of virulence. If injected in large quantities into the peritoneal cavity of a guinea-pig it is capable of causing death; subcutaneously, however, as a rule it is without effect. Chantemesse and Widal,[2] however, show that if in addition to injecting the bacillus subcutaneously the toxines of the streptococcus pyogenes are injected intra-peritoneally, then the virulence of the typhoid bacillus becomes greatly increased, so that after several such passages the typhoid bacillus finally becomes so pathogenic that even by itself, without the aid of streptococcus toxine, a small quantity injected under the skin is sufficient to cause death within 24 hours from general typhoid septicæmia.

[1] Delivered on March 22nd

[2] Annalesde l'Institut Pasteur, 1892, p. 759.

The toxines of the streptococcus, however, are not the only soluble poisons which, by diminishing the resistance of the organism, allow of the rapid growth and increased virulence of the typhoid bacillus. The toxines of bacillus coli and bacillus proteus vulgaris may be used instead, as Sanarelli[3] has shown. Now it is noticeable that these very micro-organisms, the toxines of which when absorbed so assist the growth and further the generalisation of the typhoid bacillus, are normal inhabitants of the human intestine. In addition, it is known that during typhoid fever they themselves, and especially the bacillus coli, rapidly increase in number, while their virulence becomes greater.[4] Lastly, in many cases of the disease their toxines *are* absorbed, for, as I shall show, it is by no means uncommon to find that the blood of a typhoid patient is also agglutinated by the bacillus enteritidis, while Lorrain Smith[5] has shown the same to be true for other varieties of bacillus coli, evidently proving that the toxines of these bacilli have been absorbed into the system.

It is evident, then, that these facts offer us a clue whereby to explain the occurrence of relapses. If in a given case at the end of the attack the immunising properties have been as yet but poorly acquired, only just in sufficient degree to destroy the majority of the bacilli but leaving others intact, and if under these circumstances a further absorption of toxines from the alimentary canal should take place, then we shall have all the conditions which will enable the typhoid bacilli to acquire fresh virulence and to re-invade the organism.

Further, the experiments of Sanarelli,[6] if they should be fully confirmed, seem to lift this view from the domain of theory into that of fact. Thus Sanarelli showed that it is quite easy to produce experimentally a relapse of the acute septicæmic typhoid fever from which animals in general suffer. All that is necessary is to inject into a guinea-pig at first a dose not quite sufficient to be fatal. The animal recovers, but for some time afterwards attenuated typhoid bacilli may still be found in the purulent focus at the seat of inoculation. If, now, in this condition a dose of toxines, either of bacillus coli or of bacillus proteus vulgaris, be injected into the peritoneum, the typhoid bacilli at once acquire fresh virulence, the organism is invaded afresh, and the animal dies from acute experimental typhoid fever. More important still, on two occasions he was able to determine such a relapse by injecting small quantities of the toxine into the stomach and so into the intestines, thus exactly reproducing the conditions occurring in the human subject.

It would seem, then, probable that auto-intoxication plays a very important part in the causation of relapses—a con-

[3] Ibid., p. 725.
[4] Ibid., 1894, p. 214.
[5] Brit. Med. Jour., Jan. 28th. 1899.
[6] Annales de l'Institut Pasteur, 1892, p. 741.

sideration, be it remarked, in favour of the antiseptic treatment of the disease and one which also emphasises the wisdom of the common practice of withholding solid food for some considerable time after the normal temperature has been reached. If this be given too early, before the digestive juices have recovered their full power, marked fermentative changes would be likely to occur in the undigested mass and thus the conditions favouring a relapse would arise.

Is, however, the rôle played by auto-intoxication limited to its connexion with relapses? May it not be of equal or even greater importance, as indeed Chantemesse and Widal suggest, in determining the primary disease? The knowledge which we now possess concerning the enormous numbers of bacilli which may be excreted from a patient suffering from typhoid fever renders it more and more evident that the typhoid bacillus is not the only factor necessary for the production of typhoid fever. Were it so no one should escape, least of all those who work at the disease. To originate the fever other factors must coöperate after the introduction of the bacillus. The gastric juice has no power to destroy the micro-organism and it therefore always passes into the intestine, and yet typhoid fever, as we see in cases of epidemics, by no means always results. May it not be that, in some cases at least, disease only follows when as the result of some trifling derangement of the bowel the soil has already been prepared by the absorption of toxic products or, in other words, by auto-intoxication?

Typhoid Fever without Intestinal Lesions.

In my first lecture, after discussing the relation which the bacillus bore to an ordinary case of typhoid fever, I showed that the evidence pointed convincingly to the view that the disease was really of the nature of a septicæmia—modified septicæmia, it is true, in that in nearly all cases the primary lesion is in a definite situation, but septicæmia none the less, in that in all cases the generalisation of the bacilli through the blood takes place, with the subsequent growth of the organism in the most diverse organs of the body. Closely connected with this more modern view of the disease is a question which has lately been exciting much interest, whether, namely, it is possible to have typhoid fever without intestinal lesions—to have, in fact, a typhoid septicæmia without a marked primary focus of disease. Evidently, from what has been said, there would seem to be nothing to prevent such a variety of the disease occurring. Indeed, we might go further and say even that we might expect it. The question is one which can only be settled finally by bacteriology, but it should not be forgotten that in reality this is no new idea. It is, indeed, as old as our knowledge of typhoid fever itself. Thus Louis[7] records among his cases one (Observation 52) in which, while clinically the case

[7] Recherches sur la Fièvre Typhoïde, deuxième édition, tome ii., p. 301.

seemed undoubtedly one of typhoid fever, yet post mortem there were no intestinal lesions. It is true that he himself refused to believe that this and similar cases were really typhoid fever, but such was not the opinion of all his contemporaries. Since the time of Louis, also, many similar cases have been reported from time to time, and of late years a certain number with bacteriological examinations. In all some 18 of the latter have now been described. Of these a considerable number, especially those of earlier date, have to be excluded for our present purpose, since the tests applied to the isolated bacilli were not sufficiently stringent. But even if we thus eliminate the cases of Vaillard,[8] Karlinski,[9] Vincent,[10] Beatty,[11] Pick,[12] Chiari and Kraus,[13] we are still left with others, which are almost certainly representatives of this group, such as, for example, those described by Du Cazal,[14] by Dr. Cheadle,[15] by Dr. Bryant,[16] by Flexner and Harris,[17] and finally by Lartigau.[18] In these cases the patients, after having suffered during life from a disease resembling typhoid fever, presented no intestinal lesions post mortem, but the typhoid bacillus was recovered from many of their organs and often from the blood of the heart as well. It is true that in none of these cases was the reaction of the isolated bacillus to high dilutions of typhoid serum investigated. Dilutions of 1 in 20, of 1 in 50, and of 1 in 100 have been made by different observers, but not higher, and a possible source of error has thereby been introduced. Still, remembering that we are not dealing with a single case but with a series of cases all of which present more or less similar characters, remembering, too, that during life these patients have often presented the typical symptoms of typhoid fever, including the presence of rose spots, and bearing in mind that some at least of them have evidently been exposed to typhoid infection, other members of the family being ill with typhoid fever at the same time, there cannot be any moral doubt that the bacilli found were in truth the typhoid bacilli and that this variety of typhoid fever does really exist. That it is uncommon is proved by the fact that at St. Bartholomew's Hospital no case has occurred during the last three years, though Widal examinations have been made in all suspicious cases as a matter of routine, and therefore such a case if it had occurred could not have been overlooked.

[8] La Semaine Médicale, March, 1890, p. 94; Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris, 1890, p. 201.
[9] Wiener Medicinische Wochenschrift, 1891, pp. 470 and 511.
[10] Annales de l'Institut Pasteur, 1893.
[11] Brit. Med. Jour., January, 1897, p. 148.
[12] Wiener Klinische Wochenschrift, 1897, No. 4., pp. 82 to 86.
[13] Zeitschrift für Heilkunde, xviii., p. 471.
[14] Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris, 1893.
[15] The Lancet, July 31st, 1897, p. 254.
[16] Brit. Med. Jour., April 1st, 1899.
[17] Johns Hopkins Hospital Bulletin, 1897, p. 259.
[18] Ibid., April, 1899, p. 55.

It is interesting to speculate on the entry of the bacillus in these cases. In this connexion an important fact strikes one on reading the records of the post-mortem examinations. It is that, though in all cases the intestine is described as being quite natural, yet in nearly all we find that the mesenteric glands were affected, being for the most part enlarged, swollen, and reddened, very much indeed as we find them in ordinary cases of typhoid fever. This would seem to suggest strongly that in these cases also the bacilli commonly enter the body through the intestine, passing, however, directly through the intestinal wall into the lymphatic glands, where they germinate and whence they become generalised as usual. The passage of micro-organisms such as bacillus coli through an apparently healthy intestinal wall is by no means uncommon. There is no reason, therefore, to doubt that a similar passage might be sometimes effected by the typhoid bacillus.

There would seem, then, to be the strongest evidence in favour of the view that sometimes, though rarely, the typhoid bacillus may pass into the blood and become generalised in the organs, just as occurs in ordinary typhoid fever, but without first causing any intestinal disease, even though, as is probable, the bacilli enter through the intestinal tract.

Typhoid Fever in the Fœtus.

In connexion with this class of cases it is interesting to notice that a very similar form of the disease is by no means uncommon in the fœtus. Indeed, fœtal typhoid fever of the primary septicæmic type is a frequent, though by no means the only, cause of the abortion which so commonly occurs during the disease. Experimentally it was shown many years age by Chantemesse and Widal[19] that the placenta formed no bar to the typhoid bacillus, and at the present time a considerable number of cases are on record in which the micro-organism has been found in the human fœtus. One of the most interesting of these is the following, observed by Dr. Andrewes, in the case of a fœtus from a woman suffering from typhoid fever, who aborted in the fourth month during the epidemic at King's Lynn. The typhoid bacillus in this instance was found in pure culture in the heart's blood and also in the spleen. Morphologically (including flagella) and culturally in all respects it resembled the typhoid bacillus while its agglutinable qualities were so marked that for a time it was used as the laboratory standard culture.

It should be noted, too, that in these cases, though the bacillus may be found in the blood and in many of the internal organs, the intestine is always natural (Etienne,[20] Freund and Lévy,[21] and Janiszewski[22]), and this indeed is

[19] Archives de Physiologie, 1887, p. 270.
[20] Gazette Hebdomadaire, 1896, p. 184.
[21] Berliner Klinische Wochenschrift, 1895, p. 539.
[22] Münchener Medicinische Wochenschrift, 1893, p. 705.

what we might expect, seeing that the bacilli having broken through the placental barrier pass directly into the circulating blood without coming first in contact with the alimentary canal. Typhoid fever, then, in the fœtus is an example of a primary typhoid septicæmia.

Local Typhoid Infection.

We have seen, then, firstly that ordinary typhoid fever consists in a primary intestinal lesion followed by a secondary generalisation of the bacilli, and, secondly, that cases may occur, very similar, clinically, in which the septicæmia is present but in which the primary focus of disease is wanting. We may now ask ourselves whether it is possible for the typhoid bacillus to produce merely a local disease without there being any symptom of general infection at all. Analogy would lead us to believe that this might be possible. Thus the pneumococcus is the specific cause of acute pneumonia, but sometimes it may produce a fatal septicæmia, and, again, in other cases it may give rise to merely a local disease such as an otitis media. As regards the first two lesions, therefore, it presents an almost exact parallel with the typhoid bacillus, and we have now to ask whether the parallel may not be drawn yet closer by an agreement on the third point. Experimentally in the lower animals there is no doubt that this is the case. Thus it has been shown by Dmochowski and Janowski [23] that in dogs and guinea-pigs, if a subcutaneous injection of typhoid bacilli be made under certain conditions no general disease follows but merely a localised abscess. We might, therefore, expect that occasionally in man a similar result might occur if from any cause the general resistance of the organism to the typhoid bacillus be increased. Two cases at least of this kind have been described and probably a third, two being examples of cholecystitis and one of cystitis. The first case to which I may refer is that of Dr. Cushing.[24] The patient was a woman, aged 26 years, who, with the exception of an attack of pneumonia 10 years before, had never had any illness whatever, the history being perfectly clear on this point. She was admitted into the hospital with pain in the right hypochondrium which had attacked her five days before and had continued since. Her temperature was 101° F., but it fell the next day to normal and remained down. The total duration of the fever therefore could not have been more than seven days at the most. The pain soon left her and a tumour, which proved to be the enlarged gall-bladder, was then felt. A fortnight later, the patient continuing well, abdominal section was performed and the gall-bladder was found enlarged, inflamed, and containing 15 stones. The typhoid bacillus was found in pure culture in the contents of the gall-bladder. The

[23] Ziegler's Beiträge zur Pathologischen Anatomie, 1895, Band xvii. Heft 2, p. 221.

[24] Johns Hopkins Hospital Bulletin, May, 1898.

patient made a rapid recovery. Here then we have a case of typhoidal cholelithiasis and cholecystitis, but without any evidence of typhoid fever, such as we understand it, having occurred at any time.

The case recorded by Dr. T. Houston[25] is also very similar. In this case the patient had suffered for three years from symptoms of cystitis. The trouble began soon after she had been nursing a child who had died from "diarrhœa," but she herself had never had at any time any illness to suggest typhoid fever. After the symptoms had lasted for three years a bacteriological examination of the urine was made. It was found to be acid, to contain some pus and typhoid bacilli in pure culture.

In the third case, one of cholecystitis, recorded by Hunner,[26] the patient's symptoms, mostly attacks of severe pain in the right hypochondrium, had lasted on and off for some three and a half years. Operation was at last performed and the gall-bladder was found to be greatly distended and to contain pus. Typhoid bacilli were obtained in pure culture from the latter. In this case, however, the patient had had what she described as "remittent fever" 18 years before, so that it is conceivable that we are here dealing with a case of prolonged retention of typhoid bacilli within the body and not a local infection. The evidence, however, seems to point to the latter.

These cases, then, lend support to the view that the typhoid bacillus is capable of causing sometimes merely a local disease, and it is probable that with the increasing number of careful bacteriological examinations now being made similar cases will soon be described.

Complications of Typhoid Fever.

We may now pass from typhoid fever itself to a consideration of the complications and sequelæ which occur so frequently in connexion with it and which form so important a part of the disease. In considering them it was impossible not to be struck with the fact that we have no very comprehensive data concerning their frequency in England, none, at all events, comparable to those collected by foreign observers, and since there is no doubt that in different countries the relative frequency of various complications differs much it seemed that it would be of interest to analyse the results of the post-mortem examinations in cases of typhoid fever which have occurred at St. Bartholomew's Hospital during the past 30 years. The results are given in Table V. In all 300 post-mortem examinations have been analysed, but, all the viscera not having been examined in each case, the percentages often depend on a smaller number. This, however, is noted in the table.

[25] Brit. Med. Jour., 1899, vol. i., p. 79.
[26] Johns Hopkins Hospital Bulletin, August and September, 1899.

TABLE V.—SHOWING THE RELATIVE FREQUENCY OF THE VARIOUS COMPLICATIONS OF TYPHOID FEVER AS THEY OCCURRED IN THE FATAL CASES EXAMINED AT ST. BARTHOLOMEW'S HOSPITAL DURING THE PAST 30 YEARS.

Note.—Every complication which was observed has been classified in the Table. Any unusual complication not mentioned may therefore be regarded as not having occurred in this series of cases.

Condition found post mortem.	Actual frequency of the condition.	Frequency per cent.
SKIN, MUSCLES, PAROTID, THYROID		
(Number of times examined, 300).		
Purpura	8	2·66
Jaundice	2	0·66
Bedsores	14	4·66
Parotitis, purulent ...	1	0·33
Goitre	3	1·00
Hæmorrhage into rectus muscle... ...	1	0·33
Idem with abscess ...	1	0·33
BRAIN		
(Number of times examined, 117).		
Natural...	107	91·45
Engorged	4	3·42
Blanched	4	3·42
Ecchymosed	1	0·85
Meningitis	1	0·85
EARS (INT.)		
(Number of times examined, 25).		
Natural...	16	64·0
Otitis media	9	36·0
HEART		
(Number of times examined, 290).		
Muscle, (*a*) natural ...	196	67·58
(*b*) parenchymatous degeneration, muscle soft and flabby ...	83	28·62
(*c*) fatty degeneration	7	2·41
Endocarditis (not rheumatic)	4	1·37
HEART (*continued*).		
Recent endocarditis in old rheumatic subjects	2	0·68
Pericarditis...	2	0·68
Ante-mortem clot in ventricle	1	0·34
Old morbus cordis ...	5	1·72
Thrombosis, pulmonary artery	1	0·34
Phlebitis	1	0·34
AORTA		
(Number of times examined, 171).		
Natural	143	83·62
"Atheromatous patches"	28	16·37
LARYNX		
(Number of times examined, 165).		
Natural	115	69·69
Inflamed (not ulcerated)...	7	4·24
Ulcerated	42	25·45
Diphtheritic membrane...	1	0·60
Perichondritis	6	3·63
Œdema of the glottis	—	—
PHARYNX.		
Ulcerated	5	—
ŒSOPHAGUS		
(Number of times examined, 178).		
Natural	177	99·43
Ulcerated	1	0·56

TABLE V.—*Continued.*

Condition found post mortem.	Actual frequency of the condition.	Frequency per cent.
LUNGS		
(Number of times examined, 295).		
Natural	89	30·16
Congested	75	25·42
Œdema	49	16·61
Congestion and œdema	29	9·83
Bronchitis (severe but without broncho-pneumonia)	8	2·71
Broncho-pneumonia	23	7·79
Lobar pneumonia ...	13	4·4
Hypostatic pneumonia	4	1·35
Subpleural hæmorrhage...	6	2·03
Pleurisy—		
(*a*) Dry	16	5·42
(1) Primary	5	1·69
(2) Secondary to other pulmonary complications ...	11	3·72
(*b*) With effusion ...	12	4·06
(1) Primary	9	3·05
(2) Secondary to other pulmonary complications ...	3	1·01
Empyema	3	1·01
Abscess	2	0·67
Infarct, hæmorrhagic	3	1·01
,, septic	1	0·33
Gangrene	1	0·33
Active phthisis ...	3	1·01

Condition found post mortem.	Actual frequency of the condition.	Frequency per cent.
INTESTINES AND PERITONEUM		
(Number of times examined, 300).		
Ulceration of large intestine	105	35·00
Idem, extensive ...	35	11·66
Appendix—		
Condition noted ...	26	—
Natural...	15	57·69
Ulcerated	11	42·30
Perforation of the intestine	94	31·33
General peritonitis from perforation ...	92	30·66
Localised peritonitis from perforation ...	1	0·33
Localised peritonitis from perforation with abscess formation	1	0·33
General peritonitis without perforation	13	4·33
Fatal intestinal hæmorrhage	23	7·66
Ascaris lumbricoides	2	0·66
Tapeworm	1	0·33
STOMACH		
(Number of times examined, 242).		
Natural or slightly engorged	234	96·69
Ecchymosed	6	2·47
Ulcerated	2	0·82

TABLE V.—*Continued.*

Condition found post mortem.	Actual frequency of the condition.	Frequency per cent.
MESENTERIC GLANDS		
(Number of times examined, 256).		
Abscess of	17	6·25
Sloughing of	1	0·39
Caseous degeneration (no other evidence of tubercle) ...	7	2·73
SPLEEN		
(Number of times examined, 292).		
Infarcts	9	3·08
LIVER		
(Number of times examined, 290).		
Natural	186	64·13
"Cloudy"	73	25·17
Fatty	28	9·65
Abscess	2	0·68
Suppuration of bile-ducts and impacted stone	1	0·34
GALL-BLADDER		
(Number of times examined, 57).		
Natural	54	94·73
Ulcerated	1	1·75
Catarrh of	1	1·75
Suppuration of (impacted stone)	1	1·75

Condition found post mortem.	Actual frequency of the condition.	Frequency per cent.
PANCREAS		
(Number of times examined, 175).		
Natural	166	94·85
"Large and soft" ...	9	5·14
SUPRARENALS		
(Number of times examined, 141).		
Natural	141	100·0
KIDNEYS		
(Number of times examined, 289).		
Natural	152	52·59
"Cloudy swelling"	111	38·40
Congestion	19	6·57
Simple infarct	1	0·34
Septic infarct; abscess	1	0·34
"Acute nephritis" ...	1	0·34
Pyelitis	1	0·34
BLADDER		
(Number of times examined, 141).		
"Natural"	134	95·03
Cystitis	7	4·96

If, now, these results be compared with those of other observers as, for example, with the elaborate statistics obtained by Hölscher[27] from the Munich records, it will at once be seen that whilst some of the figures agree well together others show the most extraordinary differences. Thus, to name a few, while broncho-pneumonia, empyema, and meningitis seem to occur as frequently in London as in Munich in connexion with typhoid fever, ulceration of the larynx is nearly five times more frequent in London, while perforation occurs in 30·6 per cent. of our cases as compared with only 5·7 per cent. in Munich. In London, that is to say, nearly one out of every three fatal cases is due to perforation; in Munich only one in 17—a truly extraordinary difference. On what exactly these great variations depend it is difficult in all cases to say, but the figures obtained at any rate clearly show the danger of believing that foreign statistics may represent even approximately the condition of affairs at home.

In considering the complications of typhoid fever one is naturally tempted to try to divide them into two great groups according as they are truly typhoidal—produced, that is to say, by the typhoid bacillus—or merely the result of a secondary infection by the pyogenic cocci. This, however, is impracticable, for, as we shall see, it is not uncommon for a given complication to be in one case homologous and in another heterologous in nature. Nevertheless certain complications are especially associated with the typhoid bacillus, and to a consideration of them I now propose to turn.

Nervous System.

Meningitis.—Two complications referable to the nervous system may occur in typhoid fever, meningitis and neuritis. Both agree in being uncommon, both, too, in being truly typhoidal. The rarity of meningitis is well shown by the fact that it only occurred once in 117 cases at St. Bartholomew's Hospital, the Munich records also in this case giving a very similar percentage. From the literature Keen[28] has collected 15 cases in which a bacteriological examination was made, and in all of them the typhoid bacillus was described as being present in the meninges and the meningeal exudation and in a considerable proportion in pure culture. Some of the cases doubtless are open to criticism, but the later ones, and especially one by Ohlmacher,[29] have been carefully worked out and may be accepted. Meningitis, then, occurring in typhoid fever, unless it be secondary to otitis media, should for the most part be regarded as directly caused by the typhoid bacillus, and to typhoid fever so complicated the term "meningo-typhoid" may be justly applied. It should be

[27] Münchener Medicinische Wochenschrift, 1891, p. 45.
[28] The Surgical Complications and Sequels of Typhoid Fever, London, 1898.
[29] Journal of the American Medical Association, 1897, p. 419.

noticed, also, that in these cases the usual clinical symptoms of meningitis, strabismus and opisthotonos, are not as a rule present, but simply delirium or profound unconsciousness and coma. It is probable, too, that if the meninges were examined more frequently, especially in cases with severe nervous symptoms, the typhoid bacillus would be found not infrequently in this situation even in the absence of definite meningitis.

Neuritis.—The pathology of neuritis occurring after typhoid fever was not at first so clear. Thus it had been found by Dr. Sidney Martin[30] impossible to produce an artificial neuritis in animals by the injection of typhoid toxines, even though these were powerful enough to give rise to fatty degeneration of the heart and to kill the animals. It was conceivable, therefore, that it might be due to some secondary infection. Recently, however, Nicholls[31] in a very careful paper has shown in the case of the rabbit, that if the bacilli themselves be injected and the dose of poison thereby be greatly increased, then neuritis follows. Experimentally, then, the typhoid poison is capable of producing neuritis, and there seems no reason to doubt that when this complication occurs in man it is in general due to a similar cause.

Respiratory System.

The complications affecting the respiratory system in typhoid fever are numerous. Among the most important we may class ulceration of the larynx, bronchitis, and pneumonia, both lobar and lobular. Of these, bronchitis and broncho-pneumonia need not detain us long, for though of very great importance clinically their pathology seems clear. They are examples of a secondary infection and are produced by the rapid growth under the influence of the fever of the pneumococci, streptococci, and staphylococci, normally present in the respiratory tract.[32]

Ulceration of the larynx.—Ulceration of the larynx, however, deserves a more special mention, both on account of its frequency (it occurred in 25 per cent. of our post-mortem examinations) and also because the condition was for long regarded as a specific part of the disease, the ulcers being looked upon as directly caused by the typhoid bacillus, in exactly the same way as are the ulcers of the intestine. The observations, however, upon which this view depended were made at a time when the widespread distribution of bacillus coli communis was unsuspected, and therefore cannot be relied upon. Moreover, the late Professor Kanthack and Dr. Drysdale,[33] in their interesting paper on this subject,

[30] Croonian Lectures, The Lancet, 1898, vol. i., pp. 1665 and 1737, vol. ii., pp. 1 and 71.

[31] Journal of Experimental Medicine, vol. iv., 1899, p. 189.

[32] Horton-Smith: St. Bartholomew's Hospital Reports, 1897, p. 46

[33] Ibid., 1895.

showed how unlikely such a view was and how much more probable it was that the laryngeal ulcers were due to secondary infection, the tissues being predisposed by the disease itself. The accuracy of this view also has been strongly supported by the fact that since their paper was written no recent observer has discovered the typhoid bacillus in the ulcerations, though bacillus coli, streptococci, and other micro-organisms have been found. There is little doubt, then, that the complication is not really specific but due to the pyogenic micro-organisms.

Lobar pneumonia.—We may now consider the pathology of lobar pneumonia occurring in typhoid fever, a complication probably rather more frequent than is generally supposed, it having occurred in nearly 5 per cent. of our fatal cases. It has been argued by some that, in certain cases at least, this complication is directly produced by the typhoid bacillus, while others hold that in all cases the pneumococcus is responsible for it, whether the pneumonia occur quite at the commencement of the typhoid fever or during its course. The matter is not a very easy one to settle finally. In the first place, it must be allowed that the typhoid bacillus may be found sometimes in the lungs even in large numbers, just as it may be found in other organs. Thus in a recent case in which infarction of the lung had occurred I obtained a pure culture of the bacillus from the infarct itself, the heart's blood, however, being sterile. There would therefore be nothing improbable in finding the specific bacilli in the consolidated lung, though this alone, of course, would not prove that they stood in causal relation with the pneumonia. In the second place, it is beyond question that in a great majority of the cases the pneumococcus is found in the lung, either alone or more rarely associated with the typhoid bacillus. This is generally admitted, and as an example it may be added that in two cases which have occurred recently at St. Bartholomew's Hospital the pneumococcus was on each occasion present, the typhoid bacillus not being found in the lung. Whenever, then, the pneumococcus is present we must attribute to it without hesitation the pneumonia, and must assume that the typhoid bacillus is present only in a secondary capacity, just as it may occur sometimes in an infarct or in a fairly normal lung. As a result, then, we must allow that without doubt the great majority of typhoid pneumonias are due to the action of the pneumococcus. A few cases, however, are on record in which the typhoid bacillus has been found in culture but in which the pneumococcus has not been obtained, in one case at least, even after the inoculation of a mouse, the most certain test for the presence of the organism. It has, therefore, been hastily assumed that in these cases at all events we have to do with true typhoidal pneumonia. If, however, these cases be carefully investigated it will be seen that, as Karlinski originally pointed out, those cases in which

the pneumococcus was not found were only examined quite late in the disease, at a time when commonly this micro-organism has already disappeared. In the very interesting case recorded by Bensaude,[34] for example, in which the patient had all the symptoms and physical signs of an initial pneumonia passing directly into typhoid fever, the exploratory puncture of the lung was only made on the tenth day. The fact, therefore, that only the typhoid bacillus could be grown from the exudation withdrawn while the pneumococcus could not be found, has but little weight. Similarly in the case recorded by Flexner and Harris[35] the patient had been ill for about two months, and from the history it would seem probable that the pneumonia started about two weeks before death. The absence here again of the pneumococcus has but little significance. At the present moment, then, we may say that no evidence exists to show that true lobar pneumonia is ever the result of the action of the typhoid bacillus. The future may conceivably reveal such cases, but before we can accept them two things are necessary: the bacteriological examination must be made early in the disease and several cultures from various parts of the diseased lung must be made. The absence of the pneumococcus, in fact, must be clearly demonstrated, not merely taken for granted as it were. If, then, the term "pneumo-typhoïde," so commonly used by French writers, be retained, it must be understood that reference is merely made to cases of typhoid fever complicated by pneumonia, and that the term does not imply that the pneumonia is typhoidal. Probably, therefore, at present it would be wiser not to use the term.

Similarly with regard to the term "pleuro-typhoïde." A few old observations are on record in which apparently the first sign of the typhoid fever was a pleural effusion, and in one case Valentini,[36] and in a second Fernet and Girode,[37] isolated, as they thought, the typhoid bacillus in pure culture. Recent observations, however, have not confirmed this discovery, so that if the term be retained it must be merely as a clinical expression and must not at present be taken to imply that the pleurisy has been directly caused by the typhoid bacillus.

Cardio-vascular System.

With the exception of phlebitis the complications referable to the heart and blood-vessels in typhoid fever are very rare, and even phlebitis in fatal cases is most uncommon. Thus in the last 30 years at St. Bartholomew's Hospital only four cases with endocarditis have come to necropsy, two with pericarditis, and one with phlebitis. The cases in which arteritis leading to gangrene has occurred have all ended in recovery. As yet the pathology of these affections is somewhat obscure.

[34] Thèse de Paris, 1897, p. 115.
[35] Johns Hopkins Hospital Bulletin, December, 1897.
[36] Berliner Klinische Wochenschrift, 1889, p. 368.
[37] Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris, 1891, p. 236.

Endocarditis.—It may be said, however, that the endocarditis is generally of the malignant type and that it is the result of a secondary infection. This, however, is not so always, for the typhoid bacillus has been found in the warty vegetations. In one case observed by the late Professor Kanthack it was so found, not however in this case alone, but in conjunction with the pyogenic cocci.

Arteritis.—Of arteritis, the common cause of that dreaded though fortunately very rare complication, spontaneous gangrene, it is difficult to speak with certainty, owing to the extreme difficulty in obtaining material. In a recent case of typhoidal meningitis, however, described by Ohlmacher,[38] produced by the presence of the typhoid bacillus, marked acute endarteritis of the meningeal vessels was found. It is, therefore, probable that when the affection attacks the peripheral vessels it may have a similar pathology and may be due directly to the specific micro-organisms, or their toxines, and not to any secondary infection. It is likely, too, that if the state of the peripheral vessels were more carefully and frequently examined a mild degree of the condition would not uncommonly be found.

Phlebitis.—With regard to phlebitis a considerable number of recent observations have been made (Vincent[39]) and in many of the cases streptococci and staphylococci have been found in the clot and vessel walls, suggesting that the inflammation is really septic in nature, though probably produced by micro-organisms with but a low degree of virulence.

Urinary System.

Nephritis.—The exact relation which the typhoid bacillus bears to the nephritis which in varying degrees of severity occurs so commonly in typhoid fever is hard to decide. It is certainly true that the typhoid bacillus may be present in the kidney after death in cases which show some evidence of nephritis, but lesions similar or even more severe frequently occur in cases in which the kidneys are sterile and in which therefore nephritis is evidently due to the excretion of toxic substances produced either by the typhoid bacillus alone or combined with those of other micro-organisms in cases where a secondary infection has occurred. Melchior[40] thus in his monograph records three cases of nephritis in which casts were found in the urine but in which in two cases the urine was sterile during life, showing that the kidneys could not have harboured the bacillus, while in the third case, which ended fatally, cultures proved the absence of the bacillus in the kidneys after death. The conclusion at which we may arrive, then, is that nephritis

[38] Loc. cit., vide note 29.
[39] La Semaine Médicale, 1895, p. 377.
[40] Cystitis und Urininfection, Berlin, 1897.

in typhoid fever is no proof of the presence of the bacillus in the kidneys. The toxines of the typhoid bacillus alone (or in combination with those of other micro-organisms) are quite sufficient to account for the majority of cases of nephritis which occur in typhoid fever. In some cases, however, in addition the bacillus may be present in the kidneys and will tend therefore to aggravate the condition.

Nephritis directly produced by the typhoid bacillus.—Very occasionally, indeed, cases of typhoid fever do occur, complicated by marked nephritis, in which it seems that the inflammation is directly produced by the local growth of the bacillus. The best known case of the kind is that reported by Thue[41] as early as 1889, in which on the thirteenth day the patient was found to be suffering from hæmorrhagic nephritis and in which post mortem the typhoid bacillus, as it was believed, was found in pure culture in the spleen and kidneys. The date of this observation, however, forbids us to place implicit confidence in it. Recently, however, a somewhat similar case has occurred at St. Bartholomew's Hospital. The patient, a man aged 22 years, who was under the care of Dr. Hensley, was taken ill on Dec. 21st, 1899, with pain and difficulty in micturition. He, however, continued his work until Dec. 30th, the ninth day of his illness. On Jan. 1st, 1900, he was admitted and was found to be suffering from typhoid fever (spots being present and the Widal reaction positive) and also nephritis. The urine contained blood, *very many casts*, a good deal of pus, and one-tenth of albumin. On Jan. 3rd (the thirteenth day) it was examined bacteriologically and was found to contain a pure cultivation of typhoid bacilli. The patient had a severe attack of fever, complicated by laryngitis. The temperature reached normal on the thirty-fourth day. The nephritis continued throughout the illness and the bacilli still persisted in the urine in undiminished numbers. (For exact details concerning the date and number of the observations made on the urine compare Table VI., Case 17*a*, and Appendix, Case X.) On the thirty-fifth day, the day after the temperature had reached normal, the urine under the administration of urotropin was freed from bacilli and the thick deposit of pus which had hitherto been present (typhoidal cystitis). After a few days, also, the casts became less and with the albumin gradually disappeared. It would seem, then, that in this case the nephritis stood in direct relation to the typhoid bacilli, for, apart from the striking effect of treatment, the improvement in the condition dating almost directly from the elimination of the bacilli, it seems difficult to ascribe so marked a nephritis observed on the eleventh day, and undoubtedly present earlier, to toxines only. Moreover, the bacilli were evidently present in the urine and kidneys from a very early period of the disease. They were cultivated

[41] Charcot: Traité de Médecine, tome i., p. 775.

first on the thirteenth day, but the first symptom which drew the patient's attention to his condition was some pain and difficulty in micturition, due doubtless to typhoidal cystitis, and evidencing the presence of the micro-organisms even at this earlier stage. For these reasons, then, we must regard the case as one of true typhoidal nephritis, or in its truest sense one of "nephro-typhoid." The extremely early date at which the generalisation of the bacilli must have occurred is of great interest.

Typhoid Bacilluria and Cystitis.

I may now pass to the bladder and the urine in typhoid fever. In drawing attention to the presence of the bacilli in the urine some little time ago[42] I was only able to prove without doubt the existence of the condition and could not venture at that time to state how frequent its occurrence might be. Lately, however, I have had the opportunity of examining a larger series of cases and the results of my observations I now bring forward. They are recorded in Table VI., p. 52. It will be seen from it that in all 45 cases of typhoid fever have been investigated. In 28 of these, though examined on several occasions, the urine was never found to contain typhoid bacilli, while in 17 the bacilli were found. This would give apparently a percentage of nearly 38 for the positive results. It is, however, undoubtedly too high, for out of the 17 positive results six were cases in which the abnormal condition of the urine had attracted attention and in which a bacteriological examination was therefore requested. Eliminating these, then, we find that 39 typhoid fever cases have been taken at random in the wards and the urine examined on several occasions. Of these cases 28 never contained typhoid bacilli, while 11 contained them in large quantities, constituting a percentage of 28. In London, then, at all events it will probably be correct to say that at least 25 per cent. of all cases present this serious and dangerous condition. This conclusion is also supported by the fact that it agrees approximately with the results obtained by Richardson.[43] This observer, working in Boston, examined the urine in 102 cases of typhoid fever, and in 23 he was able to isolate the bacillus, obtaining therefore a percentage of 22·5. At the present time, then, the evidence would show that the condition is one frequently met with and that it probably occurs in one out of every four typhoid fever patients.

Naked-eye recognition of typhoid "bacteriuria."—An important point, also, in connexion with the condition is the fact that very commonly the bacilli are present in enormous numbers, so that the urine is rendered turbid. I was at first inclined to regard these cases as rare, but really they are the

[42] Transactions of the Royal Medical and Chirurgical Society, 1897.
[43] Journal of Experimental Medicine, vol. iii., May, 1898, and vol. iv., January, 1899.

rule rather than the exception. Thus out of 14 recent cases in which this point was especially looked for, in 12 I found that the urine was turbid with bacilli, while in two only was it noted as "clear," and the microbes were accordingly first discovered on cultivation. The enormous numbers in which the micro-organisms may be present, though it increases the danger of the complication, brings with it the advantage that the condition can be recognised, or rather suspected, more easily. Indeed, this can often be effected by the naked eye. All that is necessary is to pour the turbid urine into a test tube and then holding it up to the light gently to shake it. If the turbidity be due to the presence of micro-organisms we notice at once a curious shimmer in the liquid exactly comparable to that seen in shaking any turbid broth culture, a phenomenon which, as Krogius first pointed out, is not seen when the urine is cloudy from other causes, such as phosphates, urates, &c., probably because the amorphous particles of which these deposits consist are unable to catch and reflect the light in the same way as the regularly shaped bodies of the bacteria. If, then, in a turbid typhoid urine this curious shimmer is seen it may at once be predicted that the urine is full of micro-organisms, and the typhoid bacillus should be at once suspected, for experience shows that when this condition is noticed in typhoid fever, *if the case be a male*, it is most commonly due to the presence of the true typhoid bacillus. This, however, can only be proved by cultivation, and even in the male the same naked-eye appearance may sometimes, though much less commonly, be produced by other microbes, such as the bacillus coli communis, the streptococcus pyogenes, and the staphylococcus aureus. In the female, however, much less reliance can be placed on a mere inspection of a naturally passed urine, the sources of contamination being too gross.

Conditions governing the appearance of the bacilli.—The conditions under which typhoid bacilluria occurs are subject to great variation. Thus, the bacilli may make their first appearance in the urine at any period of the disease, from the early days of the fever down to a time when convalescence is already established. The earliest date on which I have myself isolated them was the thirteenth day, and in this case they had undoubtedly been present from a much earlier period. The latest date, on the contrary, on which I have known them first to occur was the fourteenth day of convalescence. Speaking generally, however, we may say that the condition is rare before the third week of the disease. After this it may occur at any time during the fever, but not uncommonly its occurrence is delayed until the early days of convalescence. It is, therefore, much more closely associated with the later stages of the disease. The duration of the bacilluria also varies much, but it nearly always persists for some considerable time. The shortest duration recorded is eight days, but in four other cases it had

TABLE VI.—SHOWING THE FREQUENCY OF TYPHOID BACILLURIA AND THE PERIOD OF THE DISEASE AT WHICH IT OCCURS, BUT, EXCEPT IN THE FIRST TWO CASES, NOT ITS DURATION. IN THE REMAINDER, EXCLUDING THE THREE FATAL CASES, AFTER THE CONDITION HAD BEEN OBSERVED FOR A LONGER OR SHORTER PERIOD, IT WAS CUT SHORT BY TREATMENT (UROTROPIN).

Number of case.	Age of patient.	Sex.	Date on which cultivations from the urine were made.	Day on which the temperature reached normal.	Typhoid bacilli found.	Condition of the urine.	Remarks.
1	18	M.	10, 11, 13, 16, 19, 22, 25, 27, 31, 35, 39, 40, 41, 44, 46, 49, 51, 54, 58, 63.	41	39, 40, 41, 44, 46, 49, 51, 54, 58, 63.	Turbid with bacilli; sometimes a cloud of albumin; sometimes none.	A mild case of typhoid fever.
2	22	M.	39, 44, 47, 54, 58.	37	39, 44, 47.	Pyuria.	A severe case. The pyuria started suddenly on thirtieth day. Before this the urine had been natural.
3	18	M.	13, 15, 17, 23.	Fatal.	15, 17, 23.	Clear; no albumin.	Died on the twenty-third day from perforation.
4	18	M.	28.	,,	28.	—	Died on the twenty-eighth day with marked typhoid septicæmia.
5	31	M.	19.	,,	19.	Turbid with bacilli; one-seventh albumin.	Died on the nineteenth day from "heart failure."
6a[1]	29	F.	50 (R), 52 (R), 56.	56	50 (R), 52 (R).	Pyuria; turbid with bacilli.	A serious case of typhoid fever; the pyuria started suddenly on the fiftieth day. Before this the urine had been natural.
7a[2]	24	M.	18, 19, 20, 21, 28, 31, 32, 33, 37, 38, 41, 46, 56.	27	18, 28, 31, 32, 33, 37.	Pyuria; turbid with bacilli.	A serious case of typhoid fever.

8*a*[3]	21	M.	24, 26, 27, 35, 42, 54, 65.	28	24.	Duration of the bacilluria cut short by treatment.	Clear; thick cloud of albumin.	A case of medium severity.
9	11	M.	19, 20, 21, 23, 24, 27, 48, 51.	30	19, 20, 21, 23, 24.		Turbid with bacilli; faint trace of albumin.	A serious case.
10*a*[4]	31	M.	23, 27, 28, 29, 32, 34, 37, 44.	31	23, 27, 28, 29.		Pyuria; turbid with bacilli.	A case of medium severity.
11*a*[5]	36	M.	30, 38, 45, 58, 59, 60, 61, 62, 65, 70, 76.	53	58, 59, 60.		Pyuria; turbid with bacilli.	,,
12*a*[6]	13	M.	29, 31, 32, 33, 34, 36, 39, 46.	27	29, 31, 32, 34.		Turbid with bacilli; trace of albumin.	,,
13*b*	32	M.	38, 41, 44.	24	38, 41.		Pyuria.	A case of medium severity. The pyuria was first noticed when the temperature had been normal 14 days. Before this the urine had been natural.
14*a*[7]	6	M.	33, 34, 35, 36, 37, 39, 42.	30	33, 34, 35, 36.		Pyuria; turbid with bacilli.	A very severe case. Hæmaturia and pyuria occurred suddenly when the temperature had been normal one day. Before this the urine had been natural.
15*a*[8]	20	M.	44 (R), 46 (R), 51 (R), 52, 53, 63.	51	46 (R), 51 (R).		Turbid with bacilli; faint cloud of albumin.	A very severe case.
16*a*[9]	42	M.	14, 21, 33, 46 (R), 61, 68, 69, 72, 78.	52	61, 68.		Pyuria; turbid with bacilli.	,,
17*a*[10]	22	M.	13, 16, 25, 32, 34, 35, 36, 37, 39, 41, 44, 46, 50, 55, 60, 65, 74.	34	13, 16, 25, 32, 34, 35.		Pyuria; turbid with bacilli; much albumin; casts.	A very severe case. The patient suffered from true typhoidal nephritis.

a. For further details consult Appendix to Lecture III.; notes 1 to 10 give the numbers of the cases in the Appendix. [1] Case II. [2] Case III. [3] Case I. [4] Case IX. [5] Case IV. [6] Case VIII. [7] Case V. [8] Case VI. [9] Case VII. [10] Case X.

b. Observed by Dr. Andrewes.

(R) signifies that the observation was made during a relapse.

TABLE VI.—(*continued*).

Negative Cases.

Number of case.	Age of patient.	Sex.	Date of examination of urine.	Day on which the temperature rached normal.	Typhoid bacilli found.	Condition of the urine.	Remarks.
1	8	M.	12, 19, 31 (R), 44 (R), 53.	44	0	No albumin.	A case of medium severity.
2	13	M.	41, 62.	40	0	No albumin.	,,
3	20	M.	20, 25, 40, 48, 73.	63	0	Thick cloud of albumin.	,
4	11	M.	29, 42.	21	0	No albumin.	A mild case.
5	16	M.	9, 17, 25, 35.	23	0	,,	,,
6	39	M.	12, 18, 26, 36.	27	0	,,	,,
7	18	M.	25.	Fatal.	0	Faint cloud of albumin.	Died on the twenty-seventh day from heart failure.
8	36	M.	21, 30, 37, 51.	27	0	No albumin.	A mild case.
9	22	M.	16, 24, 31, 43.	27	0	Faint trace of albumin.	Very ill, but recovered.
10	33	M.	20, 28, 31, 34, 38, 42, 66.	35	0	From the twenty-eighth day onward the patient suffered from cystitis caused by bacillus coli.	,,

11	20	M.	38 (R), 49 (R), 59, 73.	51	0	Cloud of albumin.	Very ill.
12	18	M.	11.	Fatal.	0	,,	Died on the eighteenth day from heart failure.
13	13	M.	29, 40, 47.	30	0	,,	Very ill.
14	14	M.	11, 21, 30.	21	0	No albumin.	A mild case.
15	20	M.	13, 20, 27 (R), 34 (R), 41 (R), 51, 58.	41	0	Haze of albumin.	Extremely ill.
16	14	M.	21, 30, 47.	22	0	No albumin.	A mild case.
17	29	M.	20, 29, 36, 51 (R), 63.	52	0	Trace of albumin.	A case of medium severity.
18	21	M.	9, 12, 18.	Fatal.	0	One-fifth albumin.	Died on the eighteenth day from heart failure.
19	12	M.	18, 27, 34, 49.	25	0	No albumin.	A mild case.
20	16	M.	16, 25, 32, 48, 58.	46	0	,,	Very ill.
21	10	M.	22, 31, 39, 53.	31	0	,,	A mild case.
22	19	M.	20, 28, 35, 48.	—	0	,,	—
23	31	M.	12, 23, 27, 30.	Fatal.	0	,,	Died on the thirtieth day from lobar pneumonia.
24	21	F.	9, 12, 17.	15	0	Faint cloud of albumin.	A mild case.
25	15	M.	7, 10, 13, 15, 18, 21, 24.	21	0	,,	,,
26	28	M.	10, 12, 14, 17, 19, 21, 24, 27, 30.	22	0	Trace of albumin	,,
27	19	M.	9, 11, 13, 16, 18, 20, 24, 26, 29, 31, 34.	27	0	No albumin.	,,
28	—	M.	29, 41, 54.	31	0	,,	,,

(R) signifies that the observation was made during a relapse.

not disappeared until after the lapse of 21 days, 25 days, 30 days, and 70 days. Occasionally it may persist, not for months, but for years, as in a remarkable case recorded by Gwyn.[44] In this case the patient had been in hospital five years before with an attack of typhoid fever. Ever since his discharge he had had trouble with his bladder, and on re-admission five years later he was found to be suffering from cystitis and the typhoid bacillus was obtained in pure culture from his urine.

Frequency of associated pyuria.—The condition of the urine, too, offers no constant qualities. Not uncommonly, even when millions of bacilli are present, albumin is totally absent, and when present it usually does not amount to more than a trace or a cloud. In rare cases it may be present in larger quantities—one-sixth or one-seventh in two of my cases. In one case hæmaturia occurred. Although, however, albuminuria is not conspicuous in these cases it is not at all uncommon to find pus, sometimes even in considerable quantities. Thus of my 17 cases nine, or over 50 per cent., showed pyuria. The urine in nearly all cases was acid. It was never ammoniacal.

Lastly, it has sometimes been said that the cases in which typhoid bacilluria occurs are more severe clinically than those not showing this condition. Taken as a whole this is true, but it is equally true that patients may have typhoid fever of extreme severity without the urine ever becoming infected. In no case, then, we can say from the condition of the patient or from the presence or absence of albuminuria that bacilluria has occurred. We should, however, suspect it if either the urine becomes suddenly turbid and manifests the "shimmer" appearance or if pyuria occurs.

The Pathology of the Condition.

A few words may now be devoted to the pathology of this condition. How is the bacilluria produced and on what does it depend? The simplest explanation which suggests itself—namely, that we have to do with a mere filtration of the bacilli from the blood—may be at once dismissed. The extreme difficulty in finding the bacilli in the blood during life, to which I have already referred, would point to its improbability. Moreover, I have on four occasions examined the blood bacteriologically, at a time when the urine was swarming with bacilli, and on all occasions I failed to find the typhoid bacilli therein. Evidently we are not dealing with a mere filtration. A second possibility is that the condition arises from suppuration set up in the kidney by the typhoid bacillus, accompanied by the secondary passage of the bacilli and pus into the urine. Such cases of suppuration do undoubtedly occur, one being recently recorded by Flexner,[45] but they are extremely rare. Thus out of 289

[44] Johns Hopkins Hospital Bulletin, June, 1899, p. 109.
[45] Journal of Pathology and Bacteriology, 1895, vol. ii.

typhoid post-mortem examinations at St. Bartholomew's Hospital in one case only were abscesses found in the kidneys. This rare condition, therefore, could hardly explain the very frequent presence of the bacilluria.

We are driven, then, to our third possibility to offer an adequate explanation of the condition. According to this view, which I believe to be correct, the whole would depend on the rapid growth of the bacillus in the urine itself within the bladder, a stray micro-organism having found its way there from the blood, doubtless after its passage through the kidney. This explanation would seem to meet the facts of the case, for it would explain the chief peculiarities of the condition—viz., the sudden onset of the affection, the enormous numbers of the micro-organisms, and not uncommonly the total absence of albuminuria. It would also readily explain the frequency of pyuria in these cases, which would be thus due to the onset of cystitis. It has, however, by some observers been doubted whether the typhoid bacillus can grow and multiply in urine. As a matter of fact, there is no doubt that it is able to do so. Thus I found that out of six samples of urine taken and inoculated with the typhoid bacillus and then incubated at 37° C. four showed general turbidity, though varying in degree, from growth of the micro-organism at the end of 18 hours, while two did not. These latter, however, showed good growth at the end of 48 hours. The typhoid bacillus evidently, then, can grow in most urines, though the rapidity of growth varies with the specimen of the urine used. On the latter fact also doubtless in part depends the absence of the bacilli in the urine in so many cases of typhoid fever. We must believe that in every case, since the bacilli always pass into the blood, every now and then a stray bacillus is carried into the kidney and so passes into the urine. If, however, the urine be in this case not very suitable to the growth of the micro-organism, and if, too, the bladder be evacuated frequently and completely, then no harm will result, for the micro-organism will be excreted in the urine before it has time to multiply. If, however, as is often the case in typhoid fever, the patient only passes his urine at long intervals, perhaps not emptying the bladder completely, then if the urine be a favourable medium the bacillus will have ample opportunities to grow and multiply, and marked infection of the urine will result.

In addition, however, to the above considerations we have positive evidence that the *fons et origo* of the condition lies in the bladder itself. In the first place, the condition can be cured by local treatment—viz., the injection of antiseptics into the bladder. This was shown very clearly by Richardson [46] who in a given case, having failed with boric acid, was at once successful when perchloride of mercury (1 in 7000) was substituted. Gwyn [47] also has had a similar experience. Secondly, a short time ago I had the oppor-

[46] Loc. cit., vide note 43.

[47] Loc. cit., vide note 44.

tunity of examining one of these cases post mortem. The patient was a man, aged 31 years, who died on the nineteenth day of the disease from heart failure. The urine was examined a few hours before death and was found to contain one-seventh of albumin and to be strongly turbid with typhoid bacilli in pure culture. Death occurred a few hours later. At the post-mortem examination the usual intestinal lesions of typhoid fever were found. The Peyer's patches and solitary follicles were swollen and beginning to ulcerate. The spleen was enlarged and soft. The kidneys to the naked eye showed only engorgement and microscopically nothing beyond "cloudy swelling" could be demonstrated. The bladder, however, showed a few scattered hæmorrhages and its mucous membrane was slightly injected. Bacteriologically the typhoid bacilli were demonstrated by culture in the spleen, the liver, and the gall-bladder, as well as the bladder urine, but the cultures from the heart's blood, the lungs and both kidneys were sterile. I should say that four separate bacteriological examinations were made from the kidneys, two from each organ, but all four yielded absolutely negative results. In this perfectly typical case, then, there can be no doubt as to the source of the bacilli. They were not found in the blood or in the kidneys, but they were present in the urine in enormous numbers. There would seem therefore to be no reasonable doubt that a stray bacillus had passed into the urine and had multiplied there and so given rise to the condition.

If, then, this proves to be, as I believe, the true pathology of the affection we are evidently dealing with what may be called a specific "bacteriuria," meaning by this term that the urine is swarming with micro-organisms, though no definite symptoms are produced by this condition. This affection has been known for years. Indeed, it was the late Sir William Roberts[48] who first drew attention to it. His observations, however, did not attract general notice and it was not until 1894 that Krogius[49] again brought the matter forward. In the *Annales Génito-Urinaires* for that year he published eight cases of this condition all due to the presence of bacillus coli communis, and since this date other writers have confirmed his observations. Indeed, the condition is almost certainly more common than is generally imagined.

It is, however, recognised by those who have worked at this subject that no hard-and-fast line can be drawn between bacteriuria and cystitis. That is to say, that while a typical case of bacteriuria will give rise to no symptoms and will at most show under the microscope a few scattered pus cells in addition to the bacilli, there are others in which the patient may complain of slight pain in passing the urine and slight frequency of micturition, the number of leucocytes also increasing, but still not forming a deposit visible to the naked eye. Finally, these cases merge again into cases of

[48] Brit. Med. Jour., vol. ii., 1881, p. 359 and p. 623.
[49] Annales Génito-Urinaires, 1894, p. 196.

frank cystitis. Now this is exactly what is also noticed in the bacilluria of typhoid fever. According to my experience about half the cases are examples of simple bacteriuria. The patients complain of absolutely no symptoms whatever; there is no frequency of micturition and no pain accompanies the act. The urine itself swarms with bacilli and beyond this nothing can be seen abnormal in it. Under the microscope, however, an occasional pus cell can generally be found. These cases are nearly always undetected because of the absence of symptoms. There are, however, others in which, in addition to the bacilli, there is an evident deposit of pus visible to the naked eye, showing that the bladder mucous membrane has become slightly inflamed. The inflammation, however, must be very slight, for usually in these also no symptoms are manifested. Lastly, we have cases in which, while the urine remains the same—that is to say, contains bacilli and pus, but remaining of course acid, since the typhoid bacillus has no power to decompose urea—we have clinical symptoms—namely, pain and frequency of micturition and possibly tenderness over the region of the bladder. These cases of obvious typhoidal cystitis are rare. No. 6*a*, Table VI. of my series (Appendix, Case II.) was, however, such a case, and other cases have been reported, for example, by Krogius[50] and a notable one by Melchior.[51] To this latter case I should like to draw special attention, for though published in 1897 in his monograph on cystitis it was observed in 1892, and is probably the first case of cystitis due to the typhoid bacillus ever diagnosed.

How are we to explain these differences—viz., that in some cases we have merely a bacilluria and in others a true cystitis? Evidently from our knowledge of the fact that the mere presence of bacteria in the bladder is not sufficient of itself to cause cystitis. Some predisposing cause is also necessary, as, for example, some injury to the bladder walls. Now, in typhoid fever so many tissues suffer from the effects of the fever that it is not a very hazardous assumption to believe that in some cases the mucous membrane of the bladder may be damaged with the rest.

If, then, in a case of typhoid fever the bladder mucous membrane is in a natural condition and if the urine be passed at the usual intervals, then if bacilluria occurs it will remain a simple bacilluria. But should there be marked retention or should the bladder walls have been damaged in any way during the course of the disease then we have the condition in which a frank cystitis may be set up.

It is interesting to note, too, that this view receives valuable support from experiment, which shows that according as the circumstances vary the typhoid bacillus is capable of causing now a simple bacilluria, now a pure cystitis. Thus, Melchior[52] showed that if a rabbit be taken and one cubic centimetre of a broth culture of typhoid bacilli be injected into the bladder

[50] Ibid., May, 1894, p. 370. [51] Loc. cit., vide note 40.
[52] Loc. cit., vide note 40.

no symptoms follow, but a bacilluria lasting for about ten days results. If, however, immediately after the injection the penis be ligatured for some hours and retention be produced then true cystitis follows. *There can be little doubt, then, from the above considerations that typhoid bacilluria, such as we see it in the wards, is due to infection of the urine by a stray typhoid bacillus, excreted by the kidneys from the blood, and its immediate multiplication in the bladder-urine. If in addition the bladder walls have been in any way damaged, then true typhoidal cystitis follows.*

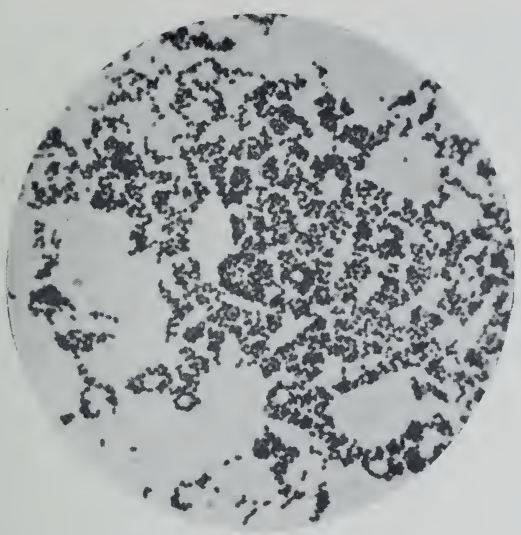
Specific bacilluria and cystitis occur, as we have seen, not infrequently in typhoid fever. It would be a mistake, however, to suppose that in every case when "bacteriuria" occurs in this disease it is due to the typhoid bacillus. As a rule, the typhoid bacillus is the microbe present, but in rare cases bacteriuria may be produced by the streptococcus pyogenes, or even by the staphylococcus aureus, facts demonstrated in the accompanying reproductions from photographs, which represent in each case the appearances seen when a drop of the urine as passed was dried on a cover-glass and stained (× 1000).

VARIETIES OF BACTERIURIA OCCURRING IN THE COURSE OF TYPHOID FEVER.

FIG. 1.

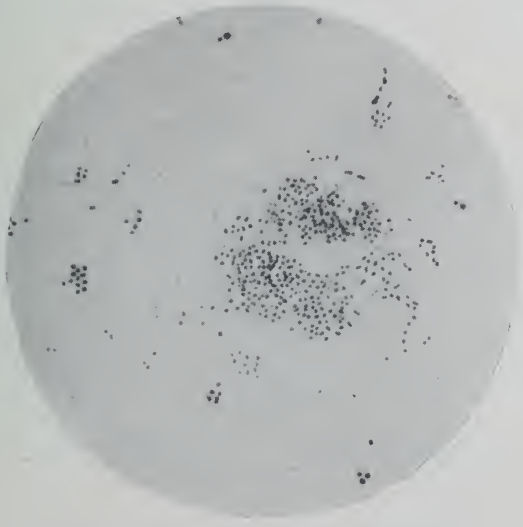
Bacillus typhosus. × 1000. (Common variety.)

FIG. 2.



Streptococcus pyogenes. × 1000. (Rare.)

FIG. 3.



Staphylococcus pyogenes aureus. × 1000. (Rare.)

Similarly, though cystitis in typhoid fever, when not the result of catheterisation, is far most commonly set up by the typhoid bacillus, we must remember that other micro-organisms may produce it. Thus cases exactly similar to the typhoidal ones may result from the invasion of bacillus coli. Indeed, it is surprising that invasions by this and other micro-organisms are not more common when we remember the opportunities offered by the ulcerated intestines.

Cholecystitis.

It is interesting to note that a very close parallel may be drawn between the relation of the bacillus to the urinary bladder and that which it bears to the gall-bladder. In the latter, just as in the former, it is not uncommon for the micro-organisms to be present in large numbers, but to give rise to no symptoms. Should, however, retention be produced or the walls irritated by the presence of gall-stones then cholecystitis follows, just as cystitis does in the case of the urinary bladder. Ten such cases have been recorded by Hunner,[53] many of them occurring at some considerable time after the attack of typhoid fever, and in all the typhoid bacillus was found at the time of operation in pure culture. Moreover, the parallelism may be pressed further, for, just as cystitis in typhoid fever will sometimes depend on the presence of bacillus coli and not on that of the specific micro-organism, so also the same may occur in the case of the gall-bladder. Thus five cases of post-typhoidal cholecystitis in which bacillus coli communis was found in pure culture in the inflamed organ are recorded in Cushing's[54] interesting paper.

Typhoidal Cholelithiasis.

In reading the record of the true typhoidal cases of cholecystitis it is noteworthy how almost constantly gall-stones were found at the time of operation. Indeed, so striking is this fact that it early led to the idea that the typhoid bacilli themselves were the cause of the cholelithiasis, and that, as a rule, it was only after the formation of the stones that the inflammation of the gall-bladder took place—a view which would well agree with the fact that not uncommonly it may be months, or even years, after the original fever before the cholecystitis occurs. The theory is supported by the fact that, as Naunyn[55] and others have shown, micro-organisms may often be found in the centre of recently formed stones,

[53] Loc. cit., vide note 26. [54] Loc. cit., vide note 24.
[55] Cholelithiasis, New Sydenham Society, 1896, p. 51.

and also by the observation of Richardson [56] that not uncommonly after death the typhoid bacilli in the bile may be found agglutinated. He observed this in five out of six cases in which he examined the bile, and although these numbers give too high a percentage they certainly prove that the condition is no uncommon one. It is easy to see how this agglutination, when it occurs, would form a nucleus round which biliary salts would be deposited and thus lead directly to the formation of stones. Recently the matter has been carried a stage further, for both Gilbert and Fournier [57] and also Richardson [58] have succeeded in producing artificial biliary calculi—the former in the rabbit by the injection into the gall-bladder of attenuated typhoid cultures and the latter in the guinea-pig by the use of already agglutinated bacilli. From the centre of Gilbert's calculus, also, typhoid bacilli in pure culture were obtained. There can be hardly any doubt, then, that the typhoid bacillus is capable of leading directly to the formation of gall-stones, and it is easy to see how the latter would assist the former in setting up the cholecystitis. If, then, inflammation of the gall-bladder occur after a case of typhoid fever, and the specific bacilli be found in pure culture, the sequence of events in all probability has been, first the formation of gall-stones and only secondly cholecystitis. In a few cases—and this is especially seen in those rare ones occurring during the fever itself—the gall-bladder may become inflamed primarily through the action of the typhoid bacillus, without gall-stones being present. But in these cases, just as with typhoidal cystitis, the walls have in all probability been damaged through the stress of the disease and the predisposing cause is therefore already present.

Suppuration in Typhoid Fever.

We may now turn our attention to suppuration in typhoid fever. In the earlier days of bacteriology all suppurations occurring in typhoid fever were regarded as due to a secondary infection by the pyogenic micro-organisms, and the experiments of Dmochowski and Janowski [59] and others, showing that experimentally the typhoid bacillus itself is quite capable of producing suppuration, came therefore somewhat as a surprise. Their correctness, however, was soon demonstrated, for it was shown that not uncommonly in man the typhoid bacillus could be obtained from the pus in pure culture. These cases have lately been collected by Keen,[60]

[56] Journal of the Boston Society of Medical Sciences, January, 1899, iii., p. 79.

[57] Comptes Rendus de la Société de Biologie, 1897, p. 936.

[58] Loc. cit., vide note 56.

[59] Loc. cit., vide note 23.

[60] Loc. cit., vide note 28.

and they show clearly that in the most diverse situations suppurations due to the typhoid bacillus have occurred. It would be a grave error, however, to suppose, as is sometimes done, that the majority of typhoid suppurations are directly due to the typhoid bacillus. This is certainly not the case; the greater number are without doubt the result of secondary infections and are produced by the ordinary micro-organisms of suppuration. This point was very clearly brought out by Vincent,[61] who in 1893 examined bacteriologically 41 cases. 32 of these cases were produced by the staphylococcus aureus or citreus, eight by the "streptococcus pyogenes either alone or in conjunction with the typhoid bacillus," and one only was produced directly by the typhoid bacillus alone. The great preponderance of cases due to the pyogenic cocci is thus well shown; and this is a point which we are apt to forget at a time when nearly every case due to the typhoid bacillus rapidly finds its way into print.

In suppuration, however, connected with bones, post-typhoidal periostitis and osteomyelitis, which Sir James Paget[62] was one of the first to describe, it is undoubtedly much more common to find the typhoid bacillus, and the reason of this is not far to seek when we remember how constant is the presence of the bacillus in the bone marrow during the disease. Keen[63] in a careful survey of the lately published cases finds that of 51 cases in which a bacteriological examination was made, 38 contained the typhoid bacillus and 13 the pyogenic micro-organisms; while Parsons[64] in six cases found the typhoid bacillus in pure culture in four cases and associated with the staphylococcus citreus in one case; in only one case did he find the staphylococcus aureus alone. At St. Bartholomew's Hospital the typhoid bacillus has not been found quite so frequently. Thus out of four cases of periostitis examined in two only was the typhoid bacillus found, once alone and once associated with the staphyloccus.

Speaking generally, however, it will be true to say that *while it is very common to find the typhoid bacillus in pure culture in the abscesses connected with bone, in suppurations occurring elsewhere its presence is undoubtedly rare.*

The following table from the records of St. Bartholomew's Hospital, the observations having been made by the late Professor Kanthack, Dr. Drysdale, or myself, demonstrates these points clearly and especially shows the rarity of the typhoid bacillus in inflammations unconnected with bone. In eight such cases examined it was not once found.

[61] Annales de l'Institut Pasteur, 1893.
[62] St. Bartholomew's Hospital Reports, 1876.
[63] Loc. cit., vide note 28.
[64] Johns Hopkins Hospital Reports, 1895, p. 417.

TABLE VII.—*Typhoid Suppurations.*

No.	Nature of the suppuration.	Micro-organisms found.	—
1	Periostitis, sternum.	Typhoid bacillus (pure culture).	—
2	,, right tibia.	Typhoid bacilli + staphylococci.	—
3	,, left tibia.	"No typhoid bacilli."	Typhoid bacilli not present.
4	Periostitis, distal phalanx of the thumb.	"Pyogenic cocci."	
5	Parotid bubo.	Staphylococcus pyogenes aureus.	
6	Ischio-rectal abscess.	Bacillus coli and streptococci.	
7	,, ,,	Streptococci.	
8	Subcutaneous abscess.	Staphylococcus pyogenes aureus and albus.	
9	,, ,,	Staphylococcus pyogenes aureus.	
10	,, ,,	Staphylococcus pyogenes aureus.	
11	Subcutaneous and intramuscular.	"Pyogenic cocci."	
12	Mammary abscess.	Staphylococcus pyogenes aureus.	

THE PERSISTENCE OF THE TYPHOID BACILLUS IN THE BODY.

There is one other point which it may be of interest now to consider, and that is, what is the length of time during which the bacillus may remain in the body? It was naturally supposed at first that as the fever passed away and as health returned the bacillus, the cause of the disease, would disappear from the tissues also. This apparently was demonstrated by the earlier observations. Thus it was shown long ago that if the spleen or mesenteric glands—the classical breeding grounds of the microbe—be examined late in the disease no typhoid bacilli are found, the organs being either sterile or possibly containing bacillus coli communis. This has been noticed by Flexner[65] as early as the sixth week, while Dr. Klein[66] has recorded it in the ninth week of the disease. The experiments of Blackstein and Welch,[67] however, showed that, sometimes at least, the typhoid bacillus might remain for much longer

[65] Johns Hopkins Hospital Reports, 1895, p. 377.
[66] Report of the Medical Officer to the Local Government Board, 1892-93.
[67] Johns Hopkins Hospital Bulletin, 1891, pp. 96 and 121.

periods in the body. Thus after intravenous injections of the bacillus into rabbits they found that the bile still contained the micro-organism when the animals died or were killed at such long intervals as 84 days, 109 days, and even 128 days after the date of inoculation. The other organs were, however, found sterile.

These experimental results in animals naturally suggested that the same thing might occur in man after typhoid fever, and this has been amply demonstrated, for we now know that it is nothing uncommon for the bacilli to remain dormant in the bile or the bone marrow for long periods, the patient, just like the experimentally inoculated animal, being meanwhile often in perfect health, and then under the influence of some passing stimulus to resume their activity and to give rise now to periostitis, now to osteomyelitis, or it may be to cholecystitis. Of the later cases belonging to the former group (bone affections) the chief interest centres round those recorded by Buschke,[68] Sultan,[69] and Bruni,[70] in which the bacilli were found in pure culture in the pus in two cases six years after the primary fever and in one case seven years afterwards. By far the most important is that of Bruni, on account of the very great care exercised in testing the isolated bacillus, so that his case may be accepted without hesitation. The patient was a woman, 36 years old, who suffered from typhoid fever in September, 1889. During convalescence she had some pain over the right tibia which lasted for some time, but which gradually disappeared. After some years, however, it returned and becoming worse she presented herself at the hospital in the year 1895 six years after her primary attack. The upper part of the right tibia was found to be swollen and reddened, and osteomyelitis was diagnosed. The bone was consequently trephined and in the centre a cavity filled with grumous pus was discovered. The contents contained the typhoid bacillus in pure culture. This case may be accepted without any doubt, and is only a type of many others recorded though not so rigorously examined. If we now turn to cholecystitis we find the same remarkable facts. Thus, to mention but a few, though many are recorded in Hunner's interesting paper.[71] In one case the bacilli were found in pure culture in the inflamed gall-bladder three months after the fever, in another eight months, and in a third after an interval of seven years. The most remarkable case of all, however, and one very carefully tested, is that recorded by Von Dungern[72] in which fourteen and a half years after the attack of typhoid fever the bacilli were still present in pure culture in the pus.

[68] Fortschritte der Medicin, 1894, p. 572.
[69] Deutsche Medicinische Wochenschrift, 1894, p. 34.
[70] Annales de l'Institut Pasteur, 1896, p. 220.
[71] Loc. cit., vide note 26.
[72] Münchener Medicinische Wochenschrift, 1897, p. 699.

Truly no longer can we say with Dr. Budd[73] that "by destroying the infectious power of the intestinal discharges the disease may be in time finally extinguished." So far, indeed, from the stools being the only agents by means of which the disease is spread they are but one of a series of agents. So far, too, from the patient ceasing to be a source of danger after his restoration to seeming health he may carry about in himself the seeds of infection for months and even years.

[73] Typhoid Fever, London, 1873, p. 180.

LECTURE III.[1]

MR. PRESIDENT AND GENTLEMEN,—In my previous lectures I have discussed the various manifestations of disease which the typhoid bacillus is able to evoke. To-day I desire to consider certain of the changes which occur in the blood during and after an attack of typhoid fever and in conclusion to refer to one point in connexion with the treatment of the disease.

The alterations which may be noted in the blood as the result of an attack of typhoid fever, as indeed of any specific infectious disease, are of two kinds. In the first place, we find gross and visible changes—changes, that is to say, relating to the number of the red and white corpuscles and to the amount of the hæmoglobin. Of these I do not propose to treat. In the second place, delicate and invisible changes—alterations which do not force themselves upon our notice but which nevertheless are of the highest importance to the organism in combating the disease, and which manifest themselves by conferring upon the blood bactericidal, lysogenic, agglutinative, and other properties. The most striking of these in typhoid fever, and the one which has most recently become known to us is the agglutinating power, and to it I propose chiefly to confine myself.

THE AGGLUTINATING POWER.

History of its discovery.—As is well known, this property was first demonstrated in the blood of patients suffering from typhoid fever by Widal in June, 1896, and the reaction, used so frequently as a means of diagnosis, has since been known by his name. It would be wrong, however, to suppose that his discovery was in all senses a new one. He, indeed, would be the last to claim it so. The great advance which Widal effected was the application to the bedside, for the diagnosis of disease, of those methods which had been perfected by other observers and notably by Gruber and Durham, but used hitherto exclusively for the identification of micro-organisms. In doing homage, therefore, to the services rendered by Widal we must not forget the work of previous observers, to which as it were he placed the keystone of the arch. The first step in the direction of this great discovery was made in 1889 by Charrin and Roger.[2]

[1] Delivered on March 27th.

[2] Charrin and Roger: Comptes Rendus, 1889, p. 710.

These observers, working with bacillus pyocyaneus, the micro-organism of blue pus, showed that if a culture were made in the serum of an animal immunised against the bacillus the growth resulting presented an unusual appearance. Instead of rendering the serum uniformly turbid, as would have been the case had a normal serum been used, the liquid remained quite clear while the growth formed a mass at the bottom of the tube. The bacilli had, in fact, become agglutinated even during their growth, though at this early date the true interpretation of the fact was not appreciated. In 1891 these facts were confirmed by Metchnikoff,[3] who also showed that similar phenomena were manifested under corresponding circumstances by the pneumococcus and the vibrio Metchnikovi. In 1894 Issaeff and Ivanoff[4] extended the law to the vibrio named after the latter.

The culture method, however, had it alone been proceeded with, would never have revealed the true importance of the phenomenon, for tested in this way it is by no means uncommon for the sera of non-immunised animals to produce similar modifications of growth. It was therefore a great step in advance when in 1895 M. Bordet,[5] one of the *Préparateurs* at the Pasteur Institute, showed that the cultivation method was unnecessary and that the agglutination occurred equally well, and indeed immediately, if the serum from an immunised animal be added to the already developed culture. It was not, however, until the following year that the full importance of the reaction became evident, when Mr. H. E. Durham[6] demonstrated that by highly diluting the serum before adding it to the culture its action was restricted to the micro-organism previously used for the immunisation of the animal. It followed, therefore, that the reaction, if properly used, was of the highest importance, for it presented us with one of our most effective means of distinguishing these micro-organisms from their numerous allies. To Gruber and Durham, then, must be given the full credit of first thoroughly appreciating the value of the reaction and working out carefully the conditions under which alone it could be used for bacteriological diagnosis.

The work of these observers had been done with the sera of animals already thoroughly immunised, and though Gruber was prepared to find the agglutinating properties present in the blood *after* an attack of typhoid fever it did not at first occur to him that the blood *during* the attack itself might also show the phenomenon. Here, then, was the opportunity of Widal,[7] who on June 26th, 1896, announced his discovery that even during the disease itself

[3] Metchnikoff: Annales de l'Institut Pasteur, 1891, p. 473.
[4] Issaeff and Ivanoff: Zeitschrift für Hygiene, vol. xvii., 1894, p. 122.
[5] Bordet: Annales de l'Institut Pasteur, 1895, p. 496.
[6] Durham: Proceedings of the Royal Society, January, 1896.
[7] Widal: Bulletins et Mémoires de la Société des Hôpitaux de Paris, June 26th, 1896.

the agglutinative power was present in the blood and that therefore the reaction could be used as a means of *clinical* as opposed to *bacteriological* diagnosis.[8] It should be noticed, however, that Widal's observation was no chance discovery. It was, indeed, directly the result of his earlier work. Four years previously he had shown in conjunction with Chantemesse[9] that the blood of typhoid fever patients even during the attack acquired considerable "preventive power," or, in other words, if injected into a guinea-pig together with an otherwise fatal dose of typhoid bacilli it was often able to prevent the death of the animal. It was natural, therefore, for him to inquire whether the agglutinative power which Gruber regarded as a sign of immunity was not also present during the disease itself. His search was successful and from it directly sprang our present method of serum diagnosis.

Such, then, is the history of this great discovery and it is pleasant to think that the credit of it belongs exclusively to no one country alone, but that it is an honour in which Frenchmen, Germans, and Englishmen may alike claim a share.

Technique.

In considering the reaction the technique to be employed is of the first importance, and in this connexion several points have to be considered relating to the dilution of the serum used, the time-limit, and the typhoid culture employed.

The dilution to be used.—As originally proposed by Widal for the "extemporaneous" or microscopical method, which is the one generally in use at the present time and to which the following remarks apply, a dilution of the serum 1.10 was adopted, one drop of the serum being, that is to say, diluted in 10 drops of culture. It was soon seen, however, that this was somewhat too low, a considerable number of cases being recorded in which a positive reaction was obtained although the patients were not suffering from, and had never had, typhoid fever. The dilution has therefore been generally raised, and the only question at issue is the exact dilution which should be decided upon. At present there is no unanimity in this matter. In Paris 1.10 is still in use, at St. Bartholomew's Hospital 1.20 is employed, Fischer (Dantzig) recommends 1.25, Neufeld in Berlin 1.30, Schumacher (Halle) 1.50, while Durham suggests 1.100 or preferably higher. It should be noted that the question is not merely an academic one. If we raise the dilution considerably—to 1.100, for example—we *ipso facto* diminish

[8] It is but just to add that anterior to the publication of Widal's discovery Dr. Grünbaum working in Vienna had *independently* observed the agglutination reaction in two cases of typhoid fever during the disease. Before, however, he could extend or record his observations Widal's fuller results were published

[9] Chantemesse and Widal: Annales de l'Institut Pasteur, 1892, p. 768.

the value of the test, for some 20 per cent. of cases *never* show a clumping power as marked as this, while others, again, only reach this height late in the disease, when the reaction is as a rule no longer needed. If, on the contrary, we choose too low a dilution we run a risk of error, of diagnosing as typhoid fever cases which are not really so. The problem before us, then, is to choose a dilution which, while reducing error to a minimum, will still enable us to diagnose nearly all cases of the disease. Without pursuing the subject further at this moment it may be said that on the whole a 1.20 *dilution* would seem from a practical point of view to attain these results in the most satisfactory manner.

The time-limit.—Another extremely important point, and one which cannot really be separated from the question of dilution, is the time-limit which should be employed. How long in doubtful cases should the serum be allowed to act on the culture before a negative or positive reaction be finally determined upon? Some authorities recommend half an hour, some one hour, some two hours, some four, or even longer. It would seem, however, that without doubt a short time-limit should be employed, one hour, perhaps, being the most suitable. It is, of course, possible that slight delayed reactions may be due to the presence of small amounts of the typhoid agglutinin, but it is equally true that they may also result from the agglutinins of other micro-organisms, such as Gärtner's bacillus enteritidis, which in small amounts would only produce an effect after some considerable time. In any case, then, a long time-limit, in addition to being inconvenient, introduces a source of danger, and therefore a limit of one hour at most may be taken as a working and safe basis.

The typhoid culture.—Lastly, with regard to the typhoid culture used, it is extremely important to select one which is agglutinated readily by appropriate typhoid serum. As I pointed out in my first lecture, if broth cultures are used most marked differences in clumping power between various typhoid bacilli can be demonstrated. The difference seems to be in some way connected with the culture media and does not mark, as a rule, any inherent difference in clumping power between various typhoid stocks, for often an agar culture from the same bacillus will clump admirably in high dilutions with the very serum which produces no effect on the broth culture. Since, however, the latter from their convenience are always now used in performing the reaction it behoves us to select a culture the clumping power of which in this medium is not diminished.

The use of dead bacilli.—It was early shown by Bordet that the reaction was by no means concerned with the life of the bacillus and that dead bacilli might be used equally

well. This point was confirmed by Widal and Sicard[10] as regards the typhoid bacillus, and they showed that perhaps formalin was the best reagent for killing the bacillus, while yet leaving its sensibility towards the agglutinating serum absolutely intact. It is easy, if Widal's directions as to the amount of formalin required be followed exactly, to confirm this observation, and it is undoubtedly correct. It might be thought, therefore, that it would be best after having found a typhoid bacillus, the 24 hours' broth cultures of which are very sensitive, to prepare a considerable quantity of such a culture and, after killing the bacilli, preserve it for general use in the laboratory. From a practical point of view, however, it may be said that while dead cultures act admirably if the agglutinating power of the serum be marked they are less satisfactory in doubtful cases, which would be returned merely as "suspicious," for owing to the bacilli being dead we no longer see those characteristic movements made by the bacilli in their efforts, as it were, to free themselves, which so often attract attention and lead us to examine the blood again a day or two later. The routine use, therefore, of dead cultures would thus seem to be hardly advisable, though for emergency use they are of great value.

What reliance to be placed on the test if performed as suggested.—We may now ask ourselves, what reliance may be placed upon the test if it be performed in the manner suggested, that is to say, *using a very sensitive 18-hour broth culture, a dilution of 1.20, and a time-limit of one hour, a "positive reaction" only being returned, when the clumping is marked and general and when the few bacilli not clumped are rendered motionless?* In the first place it may be stated that tested by experience at St. Bartholomew's Hospital, even though here as a rule a time-limit of two hours has been allowed, this low dilution does not seem to have failed. During the last three years, 1897 to 1899, the reaction has been tested and the result noted on 546 occasions. Of the cases so examined over 200 proved themselves later by their clinical course, verified not uncommonly by post-mortem examination, to be not typhoid, and yet in only a single one of these non-typhoidal cases was a positive reaction obtained. The one exception was a case of great interest. It was that of a woman who while in the hospital had symptoms resembling those of typhoid fever. The Widal reaction was returned as "just positive." At her death, however, a few days later the case proved to be one of septicæmia. No typhoid lesions were found at all nor was the typhoid bacillus found in her spleen. This organ, however, contained the staphylococcus pyogenes aureus in enormous quantities. It seemed at first sight as though the reaction was here at fault. Inquiries, however, were made by Dr. Drysdale and it was found that four months before her death the patient

[10] Widal and Sicard: Comptes Rendus de la Société de Biologie, Jan. 30th, 1897, p. 116.

had been treated at home for typhoid fever. An easy explanation was thus afforded for the presence of the agglutinating reaction during her stay in the hospital.

Objections urged to a low dilution.—So far, then, these facts would show that a 1.20 dilution, with a time-limit of one hour, is one which may be relied upon. In January, 1898, however, it was shown by Mr. H. E. Durham[11] in a very interesting paper that the serum of typhoid fever patients not uncommonly reacted strongly to the bacillus enteritidis (Gärtner) as well as to the typhoid bacillus, producing admirable clumping in both cases up to a dilution of 1.100. In higher dilutions, however, bacillus enteritidis as a rule no longer reacted, while the typhoid bacillus in general did. The two accompanying photographs (Fig. 1 and Fig. 2) illustrate this clearly. An inference which has been very commonly drawn from these facts is that in performing Widal's reaction a dilution over 1.100 should always be used, since with any lower dilution it would be impossible to be certain in any case that the agglutination of the typhoid bacillus was due to the presence of the typhoid agglutinins and not to those of Gärtner's bacillus only.

The agglutinins of bacillus enteritidis present in the blood in many cases of typhoid fever.—Of the presence of the Gärtner agglutinins in the blood in many, though by no means all, cases of typhoid fever there cannot be any doubt. The following observations made in the early part of 1898 show this clearly. In the first place, if Gärtner's bacillus were clumped only by the typhoid agglutinins present in the blood, the degree of agglutination manifested by the former should vary directly with the amount of agglutination shown by the typhoid bacillus—that is to say, whenever the typhoid bacillus is clumped in a high degree by a given serum, then the maximum dilution capable of clumping Gärtner's bacillus should rise also, though, of course, always remaining far below that of the former. Similarly the reverse should obtain with a weak typhoid serum. The two curves should, in fact, follow each other closely, though of course at a considerable distance. This, however, is not the case. The typhoid bacillus may with a given serum be clumped in a high dilution and the bacillus enteritidis only in a low dilution, while with another serum the typhoid clumping power may be less marked and that of bacillus enteritidis more marked, facts brought out clearly by the three accompanying sera charts (Case I., Case II., and Case III.). Moreover, if cases are followed into convalescence it is not an uncommon occurrence to note that after a time the serum ceases to clump the typhoid bacillus, while continuing to agglutinate Gärtner's bacillus. The two curves, in fact, become transposed, as the sera charts from Case IV. and Case V. show, a condition

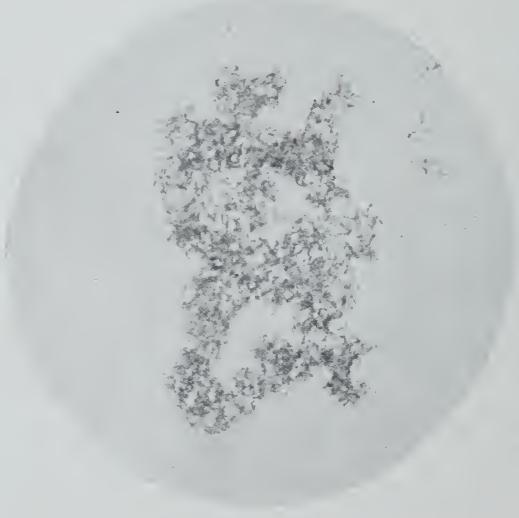
[11] Durham: THE LANCET, Jan. 15th, 1898, p. 154.

PHOTOGRAPHS SHOWING AGGLUTINATION OF THE TYPHOID BACILLUS AND ALSO OF GÄRTNER'S BACILLUS, PRODUCED BY A 1.20 DILUTION OF THE SAME TYPHOID SERUM.

FIG. 1.

(*a*) The typhoid bacillus × 250.

FIG. 2.

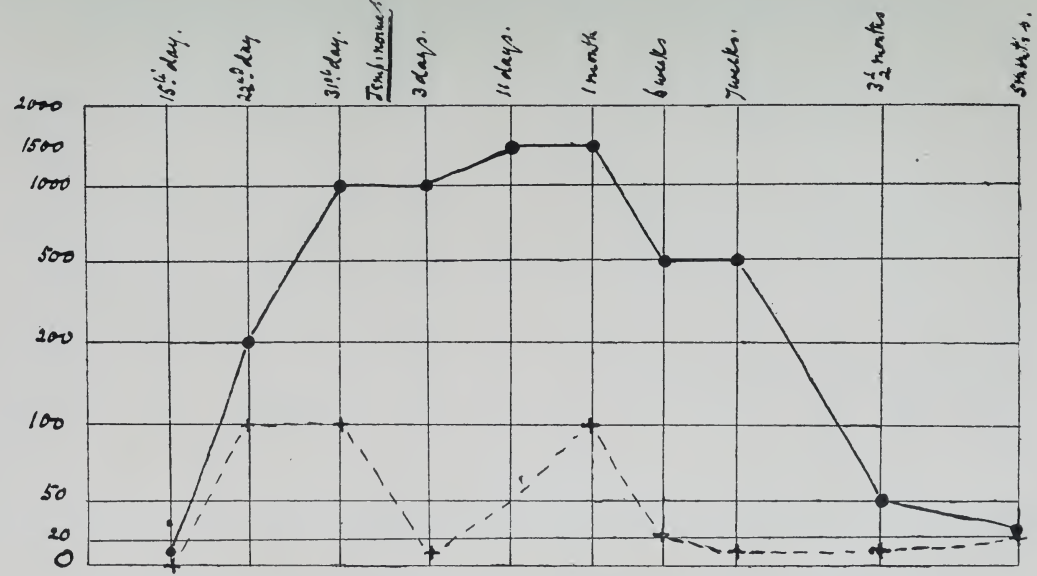


(*b*) Gärtner's bacillus × 300.

The typhoid bacillus in this case gave a complete reaction up to a dilution of 1.500, while Gärtner's bacillus did not react above 1.100.

SERA CHARTS FROM THREE CASES OF TYPHOID FEVER ILLUSTRATING THE INDEPENDENCE OF THE GÄRTNER AND TYPHOID AGGLUTINATING POWER MANIFESTED BY THE SERA IN QUESTION.

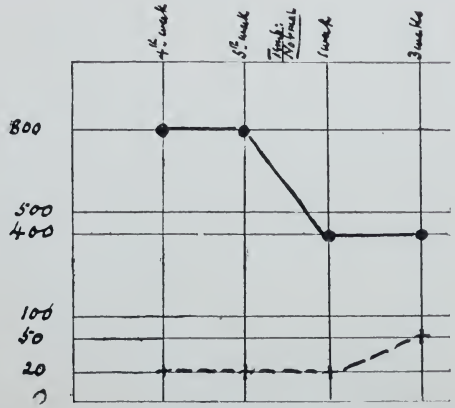
CASE I.



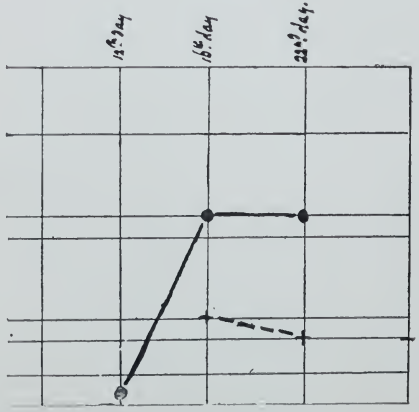
The unbroken line is the typhoid agglutination curve. The broken line is the Gärtner agglutination curve.
The figures in each case represent the maximum dilution capable of causing complete agglutination of the bacilli within one hour.

SERA CHARTS FROM THREE CASES OF TYPHOID FEVER ILLUSTRATING THE INDEPENDENCE OF THE GÄRTNER AND TYPHOID AGGLUTINATING POWER MANIFESTED BY THE SERA IN QUESTION—(*continued*).

CASE II.



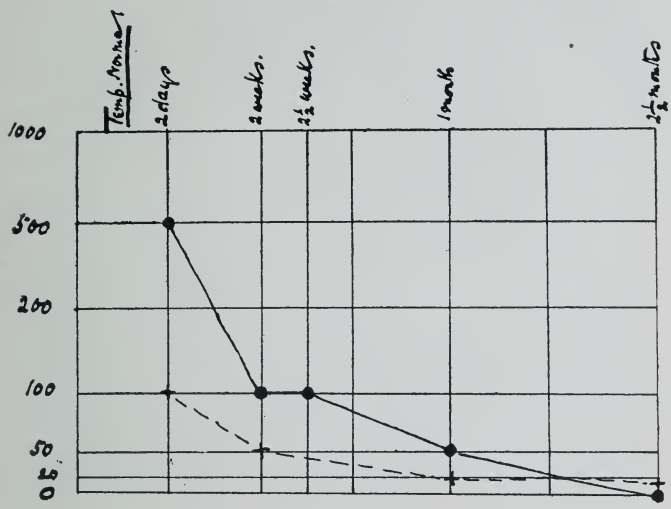
CASE III.



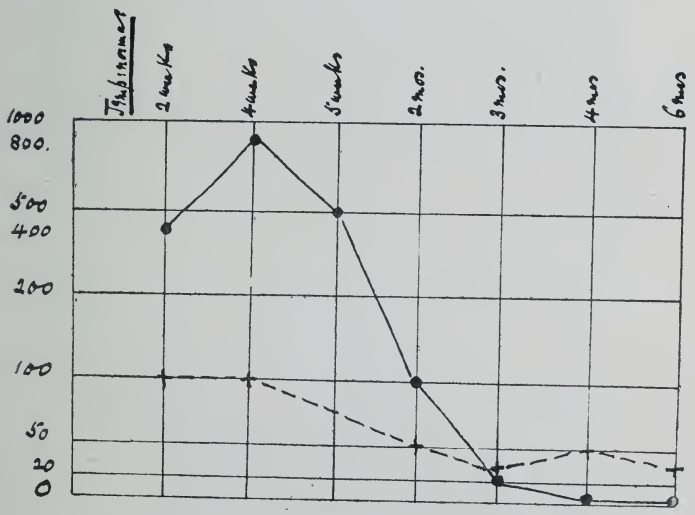
The unbroken line is the typhoid agglutination curve. The broken line is the Gärtner agglutination curve.
The figures in each case represent the maximum dilution capable of causing complete agglutination of the bacilli within one hour.

SERA CHARTS FROM TWO CASES OF TYPHOID FEVER, SHOWING THE PERSISTENCE OF THE GARTNER AGGLUTINATING POWER AFTER THE SERA HAD CEASED TO HAVE ANY EFFECT ON THE TYPHOID BACILLUS.

CASE IV.



CASE V.



The unbroken line is the typhoid agglutination curve; the broken line is the Gärtner agglutination curve.
The figures represent in each case the maximum dilution capable of causing complete agglutination of the bacilli within one hour.

of affairs which it is impossible to explain upon any other hypothesis except that of a double infection. It should be noticed, also, that the secondary infection in cases of typhoid fever is not limited to the bacillus enteritidis. Thus Lorrain Smith,[12] from observations made during the Belfast epidemic, showed that often evidence of infection by other varieties of bacillus coli could be obtained. The importance of these facts in connexion with the etiology of the disease, and especially their relation to relapses, has already been dwelt upon.

It may be accepted, then, that in many cases of typhoid fever Gärtner- as well as typhoid-agglutinins are both present in the blood. But is this any reason against using a 1.20 dilution in performing the test as has been urged? It would seem not, for, as the following experiment shows, the serum of an animal artificially immunised against Gärtner's bacillus does not completely clump the typhoid bacillus in a 1.20 dilution (microscopical method, time-limit one hour) until the serum is capable of agglutinating Gärtner's bacillus itself, at least in a dilution of 1.1000. Now such a condition of affairs rarely if ever occurs in human typhoid fever or in cases resembling it clinically. If, then, the serum of a case which suggests typhoid fever produces complete clumping of the typhoid bacillus within one hour in a dilution of 1.20 then only in the rarest cases can this be due to the presence of Gärtner and not true typhoid agglutinins.

Experiment.—A guinea-pig was immunised against bacillus enteritidis and its serum was tested as regards its clumping power from time to time against both this bacillus and against the typhoid bacillus. The following results were obtained :—

Table showing the Agglutinating Effect upon the Typhoid Bacillus of Gärtner Sera of Varying Strengths.

—	*v.* Gärtner's bacillus.	*v.* Typhoid bacillus.
a. June 28th, 1898, after three injections.	1.20 = + 1.100 = + 1.200 = 0	1.20 = 0
b. July 14th, after four injections.	1.200 = + 1.500 = + 1.1000 = trace. 1.2000 = 0 1.5000 = 0 1.10,000 = 0	1.20 = faint trace.
c. Dec. 22nd, after five injections.	1.20 = + 1.200 = + 1.1000 = + 1.2000 = partial reaction.	1.20 = + (just). 1.100 = 0 1.200 = 0

+ equals a complete reaction within one hour.

[12] Lorrain Smith : Brit. Med. Jour., Jan. 28th, 1899.

So far, then, as typhoid fever is concerned it would seem that the objections raised on the above grounds against the routine use of a 1.20 dilution, with a time-limit of one hour, are more theoretical than real—a conclusion which is supported by the results of the numerous serum observations made at St. Bartholomew's Hospital to which I have already alluded.

Rare cases in which the reaction is at fault.—It should be noticed, however, that a positive reaction obtained with a 1.20, or even a 1.40 or 1.50 dilution and a one-hour time-limit is not an absolute proof that the patient is suffering from typhoid fever. A certain number of cases have undoubtedly been recorded in which such reactions have been obtained in cases which afterwards proved themselves to be not typhoid fever. They are, however, rare, and not a few of them may have been possibly due to anterior attacks of typhoid fever, or in the earlier days to faulty technique, too long a time-limit, for example, having been allowed. Including all, however, Bensaude [13] in 1897 was only able to collect seven in which in apparently non-typhoidal cases the reaction was stated to be given in a dilution of 1.20, which, considering the thousands of cases examined, is a very small percentage of error, even if we accept them all as authentic. Since then a few other cases have been reported but they remain rare. With a dilution of 1.40, again, the reaction has proved at fault. Thus Van Oordt [14] reported the case of a man, 50 years of age, who had never had typhoid fever but whose blood reacted positively in dilutions of 1.30 and 1.40 both macroscopically and microscopically (the exact time-limit, however, is not mentioned). At the post-mortem examination the case proved to be not one of typhoid fever but of malignant endocarditis produced by the pneumococcus. Cultivation proved the absence of the typhoid bacillus. Again, using a dilution of 1.50 Kasel and Mann [15] have twice obtained the reaction in cases of pneumonia, and in both cases the reaction was "strongly positive" well within an hour. In neither case could the reaction be ascribed to a former attack of typhoid fever. How the reaction is produced in these cases is doubtful. But the fact that not uncommonly such abnormal reactions are very evanescent, being present one day and gone the next, suggests that we are really dealing with some chemical substance which happens to be temporarily present in the blood. Certain bodies, such as safranin and vesuvin, possess, as

[13] Bensaude: Thèse de Paris, p. 90.
[14] Van Oordt: Münchener Medicinische Wochenschrift, 1897, No. 13, p. 327.
[15] Kasel and Mann: Ibid., 1899, No. 18, p. 581.

Malvoz [16] has shown, a remarkable capacity for agglutinating the typhoid bacillus, and it may be that some analogous body is in these cases present in the blood.

As yet, so far as I know, no case without a history of former typhoid fever has been recorded in which with a higher dilution than 1.50 the reaction has been positive, and yet the typhoid bacillus has been proved absent by a bacteriological examination. If, then, we sum up the considerations which have been brought forward it would seem that the following conclusion is justified.

Conclusion.—For all practical purposes a *1.20 dilution with a short time-limit* (*one hour*) gives admirable results. A positive reaction so obtained has a diagnostic value about equal to that of the eruption—that is to say, that in very rare cases both may be observed in cases which are not typhoid fever. If, however, in any given case we require from the test absolute infallibility then we must use in addition greater dilutions, such as 1.100 (or even higher), employing of course the same time-limit as before—namely, one hour. But to use such dilutions as a matter of routine would be an error, since we should thereby wilfully diminish the value of the test by excluding many cases of typhoid fever (nearly 20 per cent.) which never reach even the 1.100 limit during any part of their course.

Proportion of cases in which the reaction occurs.—Supposing, then, the test be applied in this way, in what proportion of cases may we expect a positive result? Dr. J. H. Churchill, in a paper in the St. Bartholomew's Hospital Reports for 1898, analysed the cases which he had observed in the hospital during that year. He found that out of 71 cases 69 gave a positive reaction at some period of their course, giving a total percentage of 97.1. It is noticeable, also, that Widal's cases in which the blood was examined quantitatively gave an almost exactly similar result. Out of 34 cases examined 33 of them reacted positively to a dilution of 1.20, making a total percentage of 97·0. It is probable, therefore, that these numbers represent fairly accurately the true state of the case and show that in 97 per cent. of all typhoid fever cases the reaction can be obtained in a dilution of 1.20 at some period of the disease. If, however, a 1.100 dilution be used as a routine then the percentage falls very greatly. Widal's cases show that under these circumstances out of every 100 cases 17 would never show the reaction, while Lorrain Smith's cases would place the percentage of negative results even higher.

[16] Malvoz: Annales de l Institut Pasteur, 1897, p. 585.

Date of appearance of reaction.—At what date the reaction first appears is a matter very difficult to settle owing to the insidious onset of the disease. Dr. Churchill was, however, able to analyse 40 of the positive cases at St. Bartholomew's Hospital in which the commencement of the illness could be fixed, and he found that the average date of the first appearance was not later than the thirteenth day, though nine of the 40 cases gave a positive reaction between the fifth and eighth days. We may say, then, that while the reaction may occur before the end of the first week, this is unusual. It is more common for it to make its first appearance during the second week, but not rarely it may be delayed until the third or fourth week or even beyond this period.

Complete absence of the reaction throughout the disease.—It has been stated that the reaction is not to be obtained in roughly 3 per cent. of all typhoid fever cases. Possibly even this number may be too high, for conceivably some of the negative cases may not have been really typhoid fever. There is no doubt, however, that cases proved bacteriologically to be typhoid fever do exist, in which throughout the whole course of the disease no reaction can be obtained. A case of this kind was recorded by Widal in 1897[17] in which the reaction totally failed though the patient had typhoid fever followed by a relapse and in which puncture of the spleen demonstrated the presence of typhoid bacilli in this organ on two occasions. Similar cases have also since been published by Fischer[18] and Schumacher.[19] Carefully tested cases are, however, very rare and from a theoretical point of view are so important and interesting that the following cases may be shortly mentioned.

Case 1 (Rahere Ward; Sir T. Lauder Brunton).—The patient, a male, aged 18 years, was admitted with typhoid fever. He died on the seventeenth day with perforation and general peritonitis. The serum was tested in a 1.20 dilution on the eleventh and fifteenth days by Dr. Drysdale, but with a negative result. The heart's blood obtained post mortem two days later showed only a partial and incomplete reaction. At the necropsy the lesions of typhoid fever were found and the spleen and mesenteric glands contained a pure culture of typhoid bacilli, which themselves were agglutinated strongly by suitable typhoid serum. It may be argued, however, that this was merely a case of delayed appearance of the reaction. Such an objection, however, is not applicable to the next case.

[17] Widal: Annales de l'Institut Pasteur, 1897, p. 424.
[18] Fischer: Zeitschrift für Hygiene, 1899, xxxii., p. 421.
[19] Schumacher: Ibid., 1899, xxx., p. 364.

Case 2 (Mark Ward ; Dr. Church).—The patient was a male, aged 16 years. His illness began on Jan. 4th, 1898. On Jan. 12th he was admitted into the hospital with typhoid fever. The attack was prolonged, the temperature reaching normal on the thirty-fourth day. A mild attack of phlebitis, possibly combined with a relapse, followed, after which the patient made a complete recovery. Spots were never present, but in every other respect clinically the case was a typical one of typhoid fever. On the seventeenth day typhoid bacilli were found in the stools ; they reacted positively to all the morphological and cultural tests and on being tested against the serum of a highly immunised guinea-pig they gave a complete and immediate reaction in a dilution of 1.1000. The serum reaction was performed (dilution 1.20, time-limit one hour) on the 18th and 19th, the fourteenth and fifteenth days respectively, with a negative result. On the twenty-fifth day (Jan. 29th) an incomplete reaction was obtained at the end of an hour, and in this case the preparation was again examined several hours later, but showed no further change. On Feb. 21st, during the second access of fever, the reaction was again negative and on March 16th and 30th, when the temperature had been normal for 16 and 30 days respectively, similar results were obtained. In this case, then, though tested on six occasions at periods of the disease when the reaction is usually marked, on five it was found to be completely absent to a dilution of 1.20, while on the sixth occasion, though there was some clumping, the reaction could only be called indefinite. There can be no doubt, then, that in some cases proved bacteriologically to be typhoid fever it may be quite impossible ever to obtain a positive reaction, even though numerous attempts be made and at suitable periods of the disease.

Duration of reaction.—Another point of great importance to consider in connexion with the serum reaction is the length of time during which it may persist after the patient's recovery. In other words, how soon may we expect the reaction to disappear after an attack of typhoid fever? A certain number of observations have been made at varying intervals on suitable patients and the results have been sometimes negative and sometimes positive, the latter sometimes at very long intervals, many years after the primary attack. Such isolated observations, however, are always open to criticism. The only way, indeed, of settling the question how long the reaction may last is to follow a series of cases month by month until the final disappearance of the clumping power be noticed. The following cases were examined in this way. The numbers represent the highest dilution in which a complete reaction could be obtained, while the zero means that in a dilution of 1.20 no agglutination was observed. The time-limit in all cases was one hour.

Table VIII.

Case 1.—*A male, aged 16 years.*

14th day	0
15th ,, ...	0
25th ,, partial reaction	(1.20)
48th ,, ...	0

After the fever.

18 days	0
1 month	0
6½ months	0

Result.—Reaction never observed.

Case 2.—*A female, aged 18 years.*

15th day	1.20
25th ,, ... slight trace	(1.20)

After the fever.

5 days	0
14 ,, ...	0
1 month	0
2½ months	0
3½ ,, ...	0

Result.—Reaction never observed after defervescence.

Case 3.—*A female, aged 17 years.*

9th day	1.50

After the fever.

1½ months	trace (1.20)
3 ,, ...	trace (1.20)
4 ,, ...	0

Result. — Reaction disappeared within one and a half months.

Case 4.—*A male, aged 20 years.*

After the attack.

1 day	1.500
14 days	1.100
1 month	1.50
2½ months	0

Result. — Reaction disappeared within two and a half months.

Case 5.—*A male, aged nine years.*

After the fever.

3 weeks...	1.50

(Had scarlet fever.)

5 months	0
6 ,, ...	0

Result.—Reaction disappeared within five months.

Case 6.—*A male, aged 52 years.*

Beginning of relapse ...	1.100

After the fever.

10 days	1.300
4 weeks...	1.500
5 ,, ...	1.400
2 months	1.100
3 ,, ...	1.20
4½ ,, ... partial	(1.20)
6 ,, ... trace	(1.20)
7½ ,, ...	0

Result.—Reaction disappeared within five months.

Case 7.—*A male, aged 42 years.*

During the relapse	(1.20)*

After the fever.

10 days	(1.20)*
3 months	1.50
3½ ,, ...	1.40
4½ ,, ... partial	(1.20)
5½ ,, ...	0
6½ ,, ...	0

Result. — Reaction disappeared within five months.

Case 8.—*A male, aged 14 years.*

10th day	1.400
17th ,, ...	1.300
24th ,, ...	1.100

After the fever.

2 days	1.50
15 ,, ...	1.300
28 ,, ...	1.300
3 months	1.50
5 ,, ...	1.30
6½ ,, ...	1.20
8 ,, ... trace	(1.20)

Result.—Reaction disappeared within eight months.

Case 9.—*A male, aged 18 years.*

After the fever.

2 days	(1.20)*
2½ months	1.50
4 ,, ...	1.20
5 ,, ...	1.50
6½ ,, ...	1.20

* Higher dilutions not examined.

TABLE VIII.—(*continued*).

CASE 9—(*continued*).

8 months ... ... partial	(1.20)
9½ ,, ...	0

Result.—Reaction disappeared within nine months.

CASE 10.—*A male, aged 26 years.*

After the fever.

1 month	(1.20)*
8 months	(1.20)*
10 ,, ...	0
1 year	0

Result.—Reaction disappeared within 10 months.

CASE 11.—*A male, aged 22 years.*

9th day...	1.400
12th ,, ...	1.300
19th ,, ...	1.100
1st day after the attack ...	1.50
8th ,, ,, ...	1.40
4th day of relapse	1.150

After the fever.

2 days	1.400
9 ,, ...	1.400
17 days	1.150
5 weeks	1.100
3 months	1.300
4 ,, ...	1.150
5 ,, ...	1.80
6½ ,, ...	1.80
9 ,, ...	1.50
11½ ,, ... partial	(1.20)
1 year and 2 months...trace	(1.20)

Result.—Reaction disappeared within a year.

CASE 12.—*A male, aged 15 years.*

During the attack	(1.20)*
Temperature down 9 days	1.80

A relapse followed.

After the fever.

5 days	1.400
11 ,, ...	1.500
3½ weeks	1.1000
5 ,, ...	1.1000
7 ,, ...	1.800
2 months	1.300
4 ,, ...	1.200
6 ,, ...	1.150

CASE 12—(*continued*).

7½ months	1.100
9 ,, ...	1.80
11½ ,, ...	1.20
1 year and 1 month...partial	(1.20)

Result.—Reaction disappeared within 1 year and 1 month.

CASE 13.—*A male, aged 26 years.*

During the fever	(1.20)*

After the fever.

12 days	1.20
1 month	1.100
6 weeks	1.300
3 months	1.800
5 ,, ...	1.50
7½ ,, ...	1.80
9 ,, ...	1.80
1 year	1.80
1 year 2 months	1.80
1 ,, 4 ,, ...	1.30
1 ,, 6 ,, ...	1.30

Result.—Reaction still present after 1 year and 6 months.

CASE 14.—*A male, aged 16 years.*

15th day... ... ... partial	(1.20)
22nd ,, ...	1.200
31st ,, ...	1.1000

After the fever.

3 days	1.1000
11 ,, ...	1.1500
1 month	1.1500
6 weeks...	1.500
7 ,, ...	1.500
3½ months	1.50
5 ,, ...	1.30
6½ ,, ...	1.30
8 ,, ...	1.40
10 ,, ...	1.40
1 year	1.100
1 year 1 month	1.80
1 year 2½ months	1.150
1 ,, 4 ,, ...	1.80
1 ,, 5 ,, ...	1.80
1 ,, 7 ,, ...	1.40
1 ,, 9½ ,, ...	1.20
2 years	1.20

Result.—Reaction still present at the end of two years.

* Higher dilutions not examined.

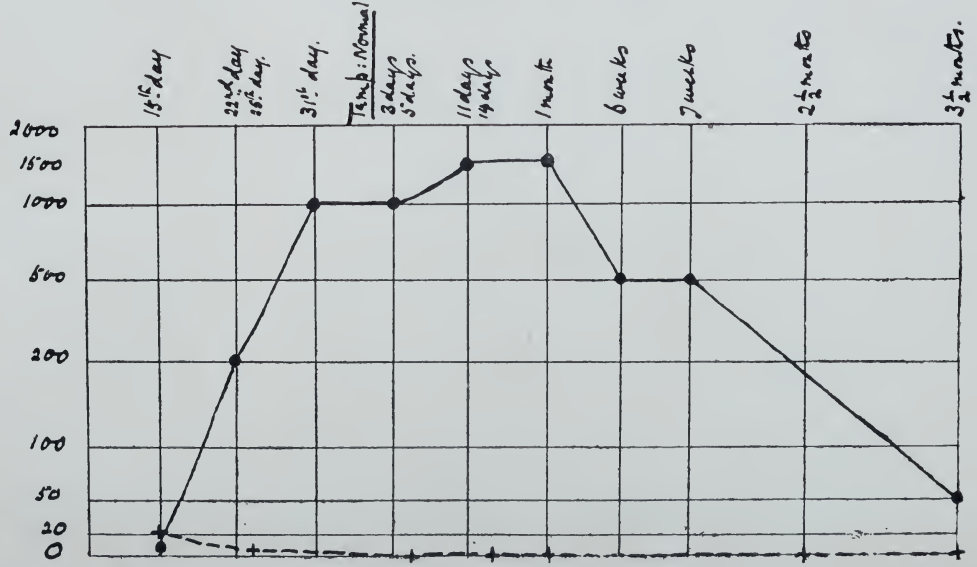
From these results it will be seen that while in the majority of the cases (12 out of 14) the reaction had disappeared by the end of a year, yet in two cases it was still present after one year and six months and two years respectively. Further, the individual cases themselves show the most marked variations in the persistence of the reaction. Thus, of the 14 cases examined in two it was never obtained after defervescence, in five others it disappeared within six months, in four more within one year, while in two it was still present at periods of one year and six months and of two years after the attack. How are we to explain these extraordinary differences? In great part, doubtless, owing to the fact that the cells of each individual organism react in a different manner to a given stimulus. We shall see that in all probability the agglutinins are produced directly by the body cells, and just as in different animals of the same species, after an injection of an equal quantity of virus, the amount of agglutinin present in the blood at the end of a given time is by no means equal, so it is not difficult to believe that the length of time during which the formation of agglutinins may continue will also vary much. But may there not be sometimes also another explanation? May not the long duration of the reaction be connected in some cases with the persistence in the body of the bacilli themselves, which, as we have seen, is by no means uncommon. Without doubt this is the explanation in some cases, but it is doubtful as yet how far the mere persistence of the reaction proves the point. At all events it has recently been shown that after typhoid inoculations in man, the dead bacilli only having been injected, the reaction may still be present for at least two years. Further continuous observations on inoculated cases are, however, much wanted. In any case in the light of these facts there would seem to be no reason at all to doubt that in certain cases the reaction may still be present even years after the attack, as in a case observed by Widal[20] in which after 26 years it was still present in a dilution of 1.30.

Serum prognosis.—It has been suggested by some observers that it is possible to base our prognosis in a case of typhoid fever on the serum reaction—to use the reaction, in fact, both as a means of prognosis as well as of diagnosis. This opinion naturally suggested itself at once to those who regarded its presence as a proof of immunity and of this school M. Courmont[21] has especially investigated the matter. In a lengthy treatise devoted to this subject he comes to the conclusion that if observations be taken frequently enough during the course of the fever, so that an agglutinating chart comparable to a temperature chart be made, then the reaction may give valuable indications for prognosis.

[20] Widal: Annales de l'Institut Pasteur, 1897, p. 424.
[21] Courmont: Thèse de Lyon, 1897.

DIAGRAM 6.

THE MARKEDLY DIFFERENT SERA CHARTS FROM TWO CASES OF TYPHOID FEVER WHICH WERE CLINICALLY ALMOST IDENTICAL, ILLUSTRATING THE VERY SLIGHT PROGNOSTIC VALUE WHICH CAN BE PLACED ON THE REACTION.



The figures in each case represent the maximum dilution capable of causing complete agglutination of the typhoid bacilli within one hour.

It is evident, however, that, even if thought desirable, such a practice would be very difficult to carry out as a matter of routine in our best-appointed hospitals, while in private practice it would be even less feasible. Moreover, a careful perusal of Courmont's work itself cannot but leave one very sceptical as to the truth of his propositions. Certainly, too, so far as my own observations extend, I have seen nothing which lends support to his views. The two following cases (Diagram 6), indeed, seem to demonstrate clearly that if we were to rely much in giving a prognosis on the amount of the agglutinating power acquired by the serum we should not uncommonly go astray. The two cases are of interest because the patients were both of the same age (16 years), and both were in-patients of St. Bartholomew's Hospital at the same time suffering from typhoid fever. Their cases could therefore be well compared. Clinically the two cases were almost exactly similar. In both the attack was long continued, lasting in the one case 35 days and in the other 31 days. In both there was also an absence of delirium and the so-called "typhoid state" and in both there was constipation. In neither case was the attack followed by a relapse, but on the contrary uninterrupted recovery took place. The cases, then, clinically were exactly similar, but, as the reproductions show, the most marked differences were exhibited by the sera charts, for while in the one case the reaction reached a height of 1.1500 in the other it was never present in dilutions greater than 1.20, and was for the most part totally absent.

It is evident, then, that a very weak serum reaction even in a severe case is no bar to a complete recovery and should not therefore indicate a bad prognosis. Again, it has been thought that a low serum reaction at the end of the attack may suggest the probability of a relapse. None, however, occurred in the case which has just been quoted, in which the reaction was absent at this period of the disease. Also if the reaction in Cases 8 and 11 (Table VIII.) be compared it will be seen that while in both cases immediately after the attack the reaction fell to 1.50, in the latter only a relapse followed, the former proceeding at once to recovery. The only conclusion, then, which can be drawn from these facts is that no certain prognosis should be based on the intensity or the reverse of the serum reaction, and that consequently quantitative measurements, except for diagnostic purposes, are of but little value.

The Origin and Nature of the Agglutinating Substance.

We have thus far studied the agglutinating reaction from the practical point of view. Let us now turn and examine it from its theoretical aspect and consider what is the nature and the mode of origin of the agglutinating substance, and, finally, what is the meaning of the reaction. On some of

these points it is impossible as yet to speak with certainty though our knowledge is steadily widening.

The agglutinin a ferment.—In the first place, as to the nature of the agglutinating substance. The evidence as yet available points strongly to the conclusion that we are here dealing with a body of the nature of an enzyme or ferment. Thus minute quantities are often sufficient to produce their effect over enormous quantities of culture. Mr. Durham, for example, was able to prepare a serum which reacted in dilutions of 1 2,000,000, or, in other words, one drop of the serum was sufficient to agglutinate over 100 litres of culture. The fact that such sera are not commonly met with would simply mean that the amount of ferment present is, as a rule, really infinitesimal. Moreover, the chemical reactions of the agglutinin associate it strongly with the ferment group of bodies. Thus the typhoid agglutinin is, like all the enzymes, extremely sensitive to the action of heat. Raising the solution to the boiling point immediately and totally destroys its action, while more prolonged exposure to temperatures higher than 65° C. produces a similar though more gradual result. Evaporation to dryness also leaves the agglutinating power intact. Again, like all enzymes, the typhoid agglutinins are completely precipitated by alcohol in excess. Ammonium sulphate also in saturation possesses a similar power, precipitating the agglutinins completely (Winterberg[22]), just as Kühne and others have shown to be the case with the majority of soluble ferments. So, too, as regards their behaviour towards dialysis, a similarity exists, for just as the enzymes are incapable of passing through the membrane so, too, is the typhoid agglutinin. For these reasons, then, it seems most probable that the typhoid agglutinin is really of the nature of a ferment—a view, moreover, which agrees well with the fact that neither putrefaction nor the prolonged action of digestive ferments, such as pepsin and trypsin, has upon it any effect.

Method of Formation of the Agglutinins.

The next question which presents itself is this, How is the ferment produced?

The view which originally suggested itself, and which probably is indeed the correct one, is that the agglutinins are secreted by the body cells, much in the same way as are the antitoxines, both bodies being produced under the stimulus afforded by the invading micro-organism. It should be noted, however, that recently a totally different theory has been put forward, according to which the agglutinins are a direct secretion of the bacilli themselves, the body cells taking absolutely no share in their formation.

The evidence upon which this view is based is interesting.

[22] Winterberg: Zeitschrift für ygiene, 1999, xxxii., p.

In the first place it is a well-known fact, as Emmerich and Löw[23] remind us, that a certain agglutination of micro-organisms does take place naturally in the cultures of not a few microbes after a certain lapse of time. In a feeble degree it is not uncommonly present even in 24-hour-old cultures, hence the necessity of examining the culture itself in performing a Widal reaction, but it becomes much more marked at a later period. Thus, for example, if a typhoid broth culture be examined at the end of three or four weeks it will be noticed that the majority of the bacilli have sunk to the bottom and that if the culture be now shaken the micro-organisms do not re-distribute themselves through the fluid but remain stuck together in large ropy masses. It might be thought that this was possibly due to the bacilli having remained so long in contact that their flagella had become entangled, but this is not so, for if a broth culture 24 hours old be taken and the bacilli be killed by the addition of four drops of formalin the culture may be kept for weeks and months and yet whenever shaken the bacilli show no tendency to cohere but are at once redistributed through the fluid and we have the appearance of a normal broth culture. The seeming agglutination can then only be due to the fact that during their growth the bacilli have been acted upon by some body which they themselves have produced and which has so altered them that they now cohere together. But are we justified in assuming that the active body in this case is really the specific agglutinin? According to M. Malvoz[24] we are, but his experiments, confined only to anthrax, are very inconclusive, and it would seem more probable that this pseudo-agglutination is rather the result of the action on the bacilli themselves of the digestive ferment which they normally secrete, and which as their vitality diminishes gradually alters and destroys them.

Another point relied upon by the supporters of the theory is that the effect of repeated bleedings on the agglutinins is said to be different from that noticed in the case of the antitoxines. As is well known, an animal whose serum has been rendered strongly antitoxic by repeated injections may be bled repeatedly in small doses to such an extent that in a short time an amount of blood equal to the total quantity in the body may be removed. If a few days later the antitoxic power of the new blood formed to take the place of the old be examined it will be found to be appreciably the same as that of the original blood, even though no further injection of toxine has been made. This fact was demonstrated first by Roux and Vaillard[25] in the case of the tetanus antitoxine, and recently Salomonsen and Madsen[26] have confirmed it for the

[23] Emmerich and Löw: Zeitschrift für Hygiene. 1899, xxxi, p. 1.
[24] Malvoz: Annales de l'Institut Pasteur, 1899, p. 630.
[25] Roux and Vaillard: Annales de l'Institut Pasteur, 1893, p. 82.
[26] Salomonsen and Madsen: Ibid., 1898, p. 783.

antitoxine of diphtheria. It can only point to fresh formation of the antitoxine from the cells of the body. Gengou,[27] however, has recently stated that as regards anthrax at least the facts are different in the case of the agglutinins, and that if an animal be bled the agglutinating power falls very rapidly and does *not* rise again. His statement is, however, based on very slender evidence and it is obvious that in a matter of such importance no such dictum could be accepted unless most fully proved.

At the present moment, then, it may be said that the positive evidence in favour of the view that the agglutinins are direct secretions of the bacilli, the organism merely playing a passive rôle during their formation, is insufficient. Moreover, various strong objections may be brought against it. In the first place, if the agglutinins are formed directly by the typhoid bacilli how can cases of typhoid fever occur in which the reaction is never present throughout the whole course of the disease? It may be argued that in these cases the agglutinin is excreted as fast as it is formed. But this explanation seems hardly sufficient when we remember that the urine, as indeed also the bile, very often shows no clumping power at all and never contains more than traces of the agglutinin even when the blood is very active. Thus in a patient at St. Bartholomew's Hospital whose blood reacted in a dilution of 1.2000 the urine showed no agglutinating power even when equal quantities were added to the typhoid culture. In another case, too, in which the blood gave a complete reaction in a 1 5000 dilution (and a trace in 1.10000) the urine agglutinated in a dilution of 1.10 but not higher. If, then, in these favourable cases the agglutinins are only excreted to so slight an extent it is difficult to believe that there are others in which the cells of the kidney excrete at once every trace of the agglutinin as soon as it makes its appearance in the blood. The occurrence then of cases of typhoid fever in which the agglutinating reaction remains totally absent constitutes a most serious objection to this theory of the formation of the agglutinins.

Again, certain facts in connexion with the agglutinating reaction itself are extremely difficult to explain on this view. For instance, it is not uncommon to find that the agglutinating reaction reaches its maximum at some considerable time after the patient is convalescent. Perhaps the best example of this is given in Case 13 (Table VIII.). In this case 12 days after the temperature had reached normal for good the maximum agglutinating reaction was obtained with a 1.20 dilution. The agglutinating power then gradually rose until three months later it had reached 1.800, after which it again began to fall. Such a fact, which is not an isolated one, can hardly be explained except by believing that the agglutinins are secretions of the body cells. For if at a time when the micro-organisms can only have been still present in very

[27] Gengou: Ibid., 1899, p. 642

small numbers (twelfth day of convalescence) the reaction only reached a height of 1.20, how could it later have reached a maximum dilution of 1.800 through the agency of the bacilli, since the latter, even if still present at this advanced stage, could not have increased in number? Lately, too, Foulerton[28] has shown that after preventive typhoid inoculations, dead cultures only being used, the agglutinating reaction may still be present in some cases for as long as two years afterwards. It is very difficult to believe that if the reaction depended on a ferment present in the liquid and directly injected at the time of the inoculation it could remain present in the body for so long a period of time, since on this view no fresh formation could take place. How, too, can we explain on this theory the fact that certain normal sera manifest sometimes a low degree of clumping power towards the typhoid bacillus? It may, of course, be assumed that such "normal" agglutinating capacity is not brought about by means of the true specific agglutinins and that bodies, perhaps analogous to safranin and vesuvin, which even in very dilute solutions can agglutinate the typhoid bacillus (Malvoz[29]) just as chrysoidin acts on the cholera vibrio (Blackstein[30]), may be present in the blood in these cases. But of this we have no evidence and the fact that the normal serum of the horse can always agglutinate both the cholera vibrio and also the typhoid bacillus and that, as Bordet[31] shows, the bodies acting on the two micro-organisms in this case are separate, distinct, and seemingly specific, points very strongly to the view that even in normal sera we are dealing with the presence of traces of the true agglutinins and that therefore they can only be formed by the body cells.

The evidence, then, at present in our possession points strongly to the view that *the agglutinins are ferments not directly secreted by the bacilli themselves but produced by the cells of the body and especially those of the spleen, the lymph glands, and the bone marrow* (Deutsch)[32] *under the influence of the stimulus produced by the invading micro-organism.*

The Mechanism of Agglutination.

Concerning the mode of action of the agglutinins—the mechanism of agglutination, in fact—we have yet much to learn. According to the view which was first put forward, the agglutinins were thought to cause the outside sheath of the bacillus to swell up and become viscoid, so that whenever the bacilli in their movements touched each other they at once cohered. This is, however, inadequate. Without doubt the bacilli are altered in some slight degree by the action of

[28] Foulerton: Middlesex Hospital Journal, October, 1899.
[29] Malvoz: Annales de l'Institut Pasteur, 1897, p. 582.
[30] Blackstein: Münchener Medicinische Wochenschrift, 1896, Nos. 44 and 45, pp. 1067 and 1100.
[31] Bordet: Annales de l'Institut Pasteur, 1899, p. 225.
[32] Deutsch: Ibid., September, 1899.

the agglutinins, though whether in the manner imagined by Gruber may well be doubted, for no swelling of the sheath can be demonstrated even by patient search in the case of the typhoid bacillus, while Roger's experiments on oïdium albicans, on which alone the theory rests experimentally, are open to criticism, since his serum in all probability contained lysines as well as agglutinins. But the mere fact that dead bacilli can be agglutinated as easily as living ones shows clearly that the clumping of the bacilli does not depend *fundamentally* on any increased adhesiveness of the sheath (even if this be present), but must be brought about rather by variations in the intermolecular forces, which result from the delicate alterations produced in the bacilli by the action of the agglutinins.

The Relation of Agglutinins to Lysines and the connexion of the former with Immunity.

Let us now consider what is the meaning of the reaction. As it occurs in typhoid fever the agglutinating reaction is obviously, as Widal has long maintained, a reaction of infection, for it is produced as a direct result of the invasion of the typhoid bacillus. But may it be more? May it also have a connexion with immunity, as Gruber has from the first believed, and may we thus reconcile to some extent the two diverging views? Emmerich and Löw[33] are of this opinion, and they believe that it has the most intimate connexion with the development of the bactericidal power, on which acquired immunity and recovery from the disease so closely depend. In short, agglutination, according to them, is nothing more than the first stage in the destruction of the bacilli. Under the influence of a single enzyme the sheath, they affirm, first swells up and later the bacilli are gradually destroyed.

This view is delightful from its very simplicity, but nevertheless it presents the very gravest difficulties. In the first place, if agglutination is but the first stage in the destruction of the bacilli, and if, as seems certain, recovery in a case of typhoid fever really occurs through the development of bacteriolytic properties, then it seems difficult to understand how cases can and do recover without the blood ever acquiring agglutinating power. Further, Neufeld[34] in a case of this kind was able definitely to prove that though the serum possessed no agglutinating capacity, yet it did possess very considerable preventive or bacteriolytic power, a minute quantity of the patient's serum protecting a guinea-pig from an otherwise fatal peritoneal injection of typhoid culture, while four times the amount of normal serum had no effect on a control animal. An exactly similar result was also obtained by Pfeiffer and Kolle[35] with an anti-cholera serum.

[33] Emmerich and Löw: Zeitschrift für Hygiene, 1899, xxxi., p. 1.
[34] Neufeld: Ibid, 1899, vol. xxx.
[35] Pfeiffer and Kolle: Centralblatt für Bakteriologie, 1896, vol. xx., p. 129.

The serum in this case possessed no agglutinating properties whatever, but bacteriolytic qualities to a remarkable degree.

It is obvious, therefore, that a serum may be strongly bactericidal without being agglutinative at all. The reverse also may occur. It may agglutinate strongly but possess no bacteriolytic properties. This was first shown by Fränkel and Otto,[36] who by feeding guinea-pigs on large quantities of typhoid cultures were able to render their blood agglutinative in dilutions of 1.200 and upwards, and yet out of 15 animals examined only three showed any bactericidal properties whatever. Similarly Widal and Sicard,[37] experimenting on frogs, were able to show that after an injection of typhoid bacilli the latter remained in the tissues for long periods and could 35 and 40 days later be recovered in the lymph sac alive and with their virulence unimpaired at a time when the lymph itself showed an agglutinating power of 1.1000. Lastly, the lack of correspondence between the agglutinative and preventive powers in animals inoculated with the typhoid bacillus has been clearly brought out by Deutsch[38] in his careful observations. To take but one example. If we compare the five sera in his table which had the highest preventive value (0·05) we notice that the agglutinating capacity of the same sera varied between 1.40 and 1.1500 instead of being identical in each, as on Emmerich and Löw's theory it must have been. From a consideration of these facts one result stands out clearly—namely, that agglutinins and lysines are absolutely distinct. Consequently Emmerich and Löw's theory in its original form cannot be maintained. It is true that as a rule both bodies are most often present together, so that a serum which is highly agglutinative is generally also highly bacteriolytic ; but this does not by any means always occur ; and to say therefore that because a patient's serum agglutinates therefore it *ipso facto* also contains bacteriolytic properties and that consequently the patient is protected against typhoid fever is clearly an error.

Agglutination, then, is a reaction of infection. But at present we have no direct evidence *proving* that it takes a share in the production of immunity, probable though this is. It may be, as Bordet[39] states, that agglutinated bacilli are more sensitive than others to the action of the alexines, or bactericidal bodies, and that the object of agglutination is therefore really to prepare the way for the action of the latter. This, however, is not yet proved, and meanwhile we must remember that a patient or an animal may be rendered absolutely immune to typhoid fever or cholera without the blood ever acquiring definite agglutinative properties at all, so that agglutination in the ordinary sense cannot be essen-

[36] Fränkel and Otto: Münchener Medicinische Wochenschrift, 1897, No. 39, p. 1065.
[37] Widal and Sicard: Comptes Rendus de la Société de Biologie, 1897, p. 1047.
[38] Deutsch: Annales de l'Institut Pasteur, September 1899.
[39] Bordet: Ibid., 1899, p. 225.

tial to the production of immunity. Possibly, however, even in these cases traces of the agglutinins may by slightly affecting the bacilli further the action of the lysines, and thus assist in bringing immunity about.

Bacteriolytic power.—We have seen, then, that in cases of typhoid fever the blood of the patient in the great majority of cases develops agglutinative properties. Bacteriolytic or bactericidal power is also actually acquired, as demonstrated by the observations of Chantemesse and Widal,[40] and Pfeiffer and Kolle,[41] and others. Indeed, on the acquisition of this power recovery chiefly depends. It should be noticed also that while the mode of origin of the agglutinins is open to discussion, our knowledge concerning the lysines is much more explicit. Thanks to the discoveries of Bordet,[42] Pfeiffer,[43] and Ehrlich,[44] it is now certain that for a serum to possess bacteriolytic properties two bodies must be present in it: first, a body of the nature of a digestive ferment, in no wise specific but present in minute quantities in normal serum, and to which Ehrlich has given the name "complement" or "addiment"; and secondly, the specific "immune bodies," side chains secreted directly from the cells of the body, and formed especially in the spleen, lymph glands, and bone marrow (Wassermann), as the result of the stimulus afforded by the presence of the specific micro-organism. The function of these latter bodies is to bring the addiment or digestive ferment, present only in minute traces, into direct connexion with the micro-organisms, a process effected, as Ehrlich has shown, by their possessing two different haptophoric groupings, the one impelling them strongly to unite with the bacteria (or red corpuscles in the case of hæmolysis) and the other joining them to the addiment. In this way the ferment which of itself would have but the feeblest power of acting on the bacilli, since only traces of it are present, is brought into immediate contact with the micro-organisms and its digestive action becomes at once apparent.

Antitoxic power.—Lastly, with regard to antitoxine. Is there a formation of this also and does the blood acquire antitoxic as well as agglutinative and bacteriolytic properties? At present we have no evidence whatever that such formation takes place. Sanarelli,[45] Pfeiffer and Kolle,[46]

[40] Chantemesse and Widal: Ibid., 1892, p., 768.
[41] Pfeiffer and Kolle: Zeitschrift für Hygiene, 1896, xxi., p. 203.
[42] Bordet: Annales de l'Institut Pasteur, 1895, p. 496.
[43] Pfeiffer: Deutsche Medicinische Wochenschrift, 1896, Nos. 7 and 8, pp. 97 and 119.
[44] Ehrlich and Morgenroth: Berliner Klinische Wochenschrift, 1899, No. 1 and No. 22. I am indebted to my friend Dr. Bulloch, Bacteriologist to the London Hospital, for pointing out to me the full value of Ehrlich's remarkable work.
[45] Sanarelli: Annales de l'Institut Pasteur, 1894, p. 375.
[46] Pfeiffer and Kolle: Zeitschrift für Hygiene, 1896, xxi., p. 203.

and Funck,[47] are all agreed on this point, and the result of their observations both on typhoid patients as well as on immunised animals shows that, just as in cholera, so also in typhoid fever, antitoxines if developed are formed only in such small quantities that their presence cannot be demonstrated. From analogy we should expect that some formation would take place and it may be that, though the cells secrete enough to neutralise the typhoid toxine, yet no hyper-secretion of these side chains takes place. At any rate, the fact remains that in typhoid fever the blood never acquires active antitoxic power.

Résumé.—If, then, we picture to ourselves the delicate changes which occur in the blood of a patient during the course of typhoid fever we should say that very early in the disease, as a rule during the commencement of the second week, agglutinative properties are in general acquired. But the date at which the agglutinins appear, the amount in which they may be present, and the length of time during which they may persist are subject to extraordinary variations. The reaction is undoubtedly one of infection, and its connexion with immunity, though probable, has not as yet been proved. A little later in the disease bacteriolytic properties make their appearance, and with the gradual increase in their amount the further growth of the bacilli in the body is checked, and finally the latter are gradually digested and destroyed. But even now the disease is not quite at an end, for the toxines set free by the destruction of the bacilli have first to be dealt with. In part they may be neutralised by antitoxines, but of this as yet we have no direct evidence, in part they are probably excreted by the usual channels and thus eliminated from the body.

Treatment.

During the last few years, then, our knowledge concerning the pathology of typhoid fever has materially increased. We know now that the disease consists in a general infection of the body by the specific micro-organism, instead of being a merely local disease as was once imagined. In addition to this we are beginning to gain a definite insight into the changes which take place in the blood and tissues as the result of the presence of the bacillus, and which eventually lead to the destruction of the micro-organism and recovery from the disease. Unfortunately, so far a similar advance has not as yet been made in the domain of treatment. The anti-typhoid serum, from which at first much was hoped, has not answered to its expectations, possibly because the serum so produced has only possessed bacteriolytic qualities and not antitoxic properties as well.

[47] Funck: Le Sérothérapie de la Fièvre Typhoide, Bruxelles, 1896.

Preventive inoculation.—The method of preventive inoculation, indeed, worked out by Professor A. E. Wright[48] offers more immediate prospects of success. By means of similar injections of dead cultures animals may be rendered immune against an otherwise fatal dose of the living virus through their blood having acquired the bacteriolytic and other properties which are normally present in the human organism after an attack of typhoid fever. If, therefore, the virus be properly standardised, and a sufficient dose be injected, there is every reason to believe that immunity against the disease can be regularly acquired in man, though how long this immunity may last we cannot as yet say, a mere examination of the agglutinating power of the blood being in no wise sufficient to determine the point. The results of the method so far published are at least encouraging, the percentage incidence of the disease in nearly 3000 cases having been reduced from 2·5 per cent. among the uninoculated to 0·95 per cent. among the inoculated. The mortality also was somewhat less.

The Value of Urotropin in Typhoid Fever.

In one other direction also progress has been made. Our knowledge concerning the infectious character of the urine has led almost at once to the introduction of a drug which eliminates this danger altogether. I allude to urotropin, and I desire, in conclusion, to bring before you the marvellous effects which are produced by its administration in cases of typhoid bacilluria and cystitis, though I may say at once that my own observations do but confirm the results already obtained in this field by Richardson. Urotropin is formed by the action of formalin on ammonia and was introduced six years ago into medical practice by Dr. Arthur Nicolaier[49] as a urinary antiseptic. It was soon found to have considerable value in checking the decomposition of the urine in cases of ammoniacal cystitis, the effect being due, as Dr. Nicolaier has shown, to the liberation of free formalin from the drug after its passage into the urine. It is true that in the acid cystitis produced by bacillus coli it is almost without effect, so that it cannot be regarded, as some too hastily have thought, as a specific for all forms of urinary infection. So far, however, as one variety is concerned it does deserve the name. I allude to its effect on the true typhoidal affections of the urinary tract. Attention was called to this matter last year by Richardson,[50] who in nine cases found that the typhoid bacilli rapidly disappeared from the urine after its use, and from my own observations I can now most strongly support his results.

[48] Wright and Leishman: Brit. Med. Jour., Jan. 20th, 1900, p. 121. Professor A. E. Wright: The Lancet, Jan. 20th, 1900, p. 150.
[49] Nicolaier: Zeitschrift für Klinische Medicin, 1899, p. 350 (with bibliography).
[50] Richardson: Journal of Experimental Medicine, 1899, vol. iv., p. 1.

It would be unbecoming on this occasion, even if time permitted, to describe in detail my observations—these I have placed in an appendix—but I think that the following reproductions of photographs represent more clearly than any figures can do the valuable action of the drug.

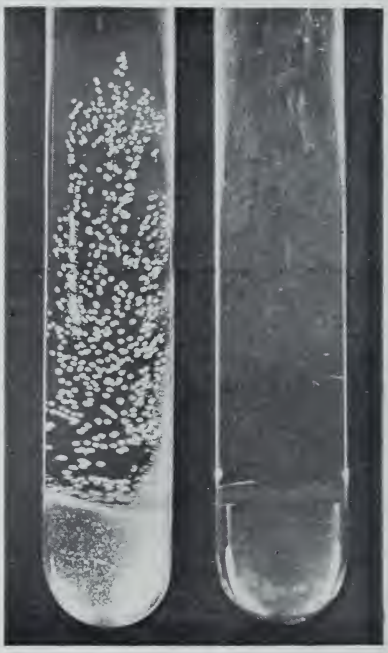
Fig. 3 (Appendix, Case I.) shows two tubes of gelatine. Tube A, that on the left, was inoculated on the twenty-fourth day of the illness with two drops of the patient's urine. A pure cultivation of what proved to be typhoid bacilli developed (the opaque atypical appearance of the colonies being due to their having sunk a little from the surface into the gelatine owing to the very hot weather). The patient was then put on urotropin, 10 grains three times a day, and on the twenty-sixth day of his illness, after 30 grains of the drug had been taken, cultures were again made. The photograph on the right shows such a one made with two drops of urine. Nothing, however, grew. The typhoid bacilli had all been destroyed and eliminated, and though the drug was stopped after 60 grains had been given, cultures made on four subsequent occasions never showed any return of the micro-organisms.

Fig. 4 (Appendix, Case VI.) shows a somewhat similar result. The photograph on the left represents a gelatine tube inoculated with a *trace* of the urine of Sept. 16th (the fifty-first day); a pure culture of typical typhoid colonies is seen. The patient was then put on urotropin (30 grains ter die) and the photograph on the right represents a gelatine tube over the surface of which *three large drops* of urine were spread, the urine having been obtained after 30 grains of the drug had been taken. The cultivation has proved sterile. The typhoid bacilli had been eliminated and destroyed. The drug was, however, continued until 120 grains had been given (four days in all), but the typhoid bacilli did not return, as proved by subsequent cultivation of the urine.

Fig. 5 (A) and (B) (Appendix, Case V.) represents the same result, but in a somewhat different way. In this case a drop of the urine itself was stained before and after the administration of 30 grains of the drug. In the one case enormous numbers of typhoid bacilli are seen, in the other none are visible. Cultures also showed their absence. The drug was continued until 120 grains had been given and was then stopped; the bacilli, however, did not return.

Fig. 6 (Appendix, Case III.) shows the marvellous naked-eye change which is produced in the urine by the administration of the drug. The photograph on the right represents the urine itself, on the eighteenth day, turbid as it was with bacilli. That on the left shows the test-tube full of urine passed on the following day after 20 grains only of the drug had been taken. It was now quite clear to the naked eye. Cultures also made with three drops of the urine showed no growth. Further examination, however, proved that in this case a few bacilli were really present, even after

FIG. 3 (APPENDIX, CASE I.).



A B

The tube on the left (Tube A) represents a gelatine tube over the surface of which two drops of urine were spread. Many typhoid colonies have developed. (The opaque atypical appearance of the colonies is due to their having sunk a little into the gelatine, owing to the very hot weather.)

On the right Tube B shows a second tube over which two drops of urine from the same patient were spread, but after 30 grains of urotropin had been taken. Nothing has grown.

FIG. 4 (APPENDIX, CASE VI.).

A B

The tube on the left (Tube A) shows a gelatine tube over which a *trace* of urine was spread. Very many typical typhoid colonies are seen.

On the right Tube B shows a second tube over which *three large drops* of urine from the same patient were spread, after 30 grains of urotropin had been taken. Nothing has grown.

(Reproduced from the *British Medical Journal* by kind permission of the Editor.)

FIG. 5 (APPENDIX, CASE V.).

a

b

Photograph *a* shows a drop of the urine dried and stained before the administration of the drug. Innumerable typhoid bacilli are seen. Photograph *b* shows a drop of the urine passed after the administration of 30 grains, dried and stained as before. No bacilli are seen and cultures proved their absence.

FIG. 6 (APPENDIX, CASE III).

On the right a test-tube full of turbid bacilluric urine is seen, on the left the clear urine passed about 18 hours later, after only 20 grains of the drug had been taken. The absence of the bacilli was confirmed by culture. (Reproduced from the *British Medical Journal* by kind permission of the Editor.)

60 grains had been taken, and that, therefore, to be quite certain of curing the condition, it would always be wise to continue the use of the drug for a week.

The photographs which I have shown happen to deal with cases of bacilluria, but in cases of typhoid cystitis, as the detailed record of the cases shows, the effect of the drug is almost as instantaneous, the pus as well as the bacilli disappearing within one, or at most two, days.

If, then, we sum up the effect of the drug on cases of typhoid bacilluria and cystitis we may say that the immediate effect of the drug is extraordinary. If the urine has been turbid before with bacilli, at the end of 24 hours—that is to say, after 30 grains have been given—the urine will now be found quite clear. Possibly cultures may reveal a few bacilli, but this is not always the case. So marked and immediate, indeed, is the effect of the drug that, if the urine is not clear at the end of 24 hours, we may at once suspect most strongly that the bacillus present is not the typhoid bacillus but one of the varieties of bacillus coli. If the drug be continued a permanent cure will be effected (unless possibly in the event of reinfection from the blood). Such a permanent cure may sometimes be effected by 60 grains of urotropin, but to make certain it would be well always to continue the drug for at least one week.

Under what circumstances, then, should the drug be given in cases of typhoid fever? Evidently whenever a urinary complication due to the typhoid bacillus has occurred. But seeing that at the present time the bacilluria and even the cystitis most often passes unnoticed from the patient complaining of no symptoms, and seeing that they are always a source of danger, the question arises whether the drug should not be given (30 grains daily) in all cases of typhoid fever, throughout its whole course and during the first three weeks of convalescence, as was first suggested by Richardson, with the intention of preventing these complications. It should be added that, taken in such doses, and during such a prolonged period, the drug produces no ill effect beyond occasionally some urethral pain if the urine is allowed to become concentrated. It may be combined, too, with any ordinary medicine, and therefore interferes in no way with the usual treatment of the disease. The routine use of the drug, therefore, would seem to be strongly indicated, for no nursing, however good, no care taken with the urine, can possibly prevent some soiling of the linen and the possible spread of infection if the case be one of typhoid bacilluria. In hospital practice, however, with good nursing the matter is of less importance. In private practice the case is very different. I do not here refer to cases treated in the houses of the rich but rather to those occurring in the squalid dwellings of the poor, to those sad cases where whole families live in single rooms, and where the spread of infection from the sick to the healthy is no fiction but an actual fact, and one, too, which is becoming more

generally recognised.[51] Since in all probability in such cases, as I have elsewhere pointed out, the urine rather than the fæces is chiefly at fault, it is permissible to hope that by eliminating the former source of danger altogether a very sensible diminution in the spread of the disease may in time be brought about.

I have now brought to a conclusion the task with which I have been entrusted. In expressing my deep sense of the honour thereby conferred upon me by the College I desire also to record my gratitude to the Physicians and Pathologists of St. Bartholomew's Hospital for the help which they have at all times given to me in my work. If I have succeeded in any way in carrying out the wishes of the founder of these lectures it is to their unvarying kindness that I must attribute my good fortune.

[51] Dr. A. Hill, the medical officer of health of Birmingham, in his report for 1898 computed that in that city during the year "*at least* 86 cases of typhoid fever, or one-seventh of the total number, were directly due to infection from another case." Others elsewhere have expressed a somewhat similar opinion.

Appendix.

The following cases of typhoid bacilluria and cystitis treated with urotropin demonstrate clearly that in this drug we possess, as Richardson first stated, an almost specific remedy. To be certain of effecting a cure the drug should be given for a week (10 grains three times a day) though often very much smaller amounts are in reality sufficient. The urine in the following cases, the patients with one exception all being males, was passed directly into a sterilised vessel, and cultures were then made on gelatine or agar. One tube received one drop of urine and a second three, or more.

Case I. (Luke Ward; Dr. Gee).—The patient was a male, aged 21 years. He had an attack of typhoid fever of medium severity. On Sept. 5th, 1899 (the twenty-fourth day), the urine was obtained and was found to be clear, acid, and to contain no albumin, but cultures made from two drops of the urine revealed a pure culture of typhoid bacilli (Fig. 3). On Sept. 6th the patient was put on urotropin, 10 grains ter die, the drug being stopped on the 8th, after 60 grains had been given. On the 7th (the twenty-sixth day of the disease) three drops of the urine proved sterile on cultivation. On the 8th (the twenty-seventh day) the same result was obtained with eight drops. The temperature reached normal on the 9th and the urine though tested by cultivation on four subsequent occasions (Sept. 16th and 23rd and Oct. 5th and 16th) never showed any return of the typhoid organisms. In this case, then, not a very severe one, the bacilli were entirely eliminated after 30 grains of urotropin and they never returned, though only 60 grains were given in all. The following case is also somewhat similar, though unfortunately it was not followed up after the cessation of the drug.

Case II. (Hope Ward; Dr. Gee).—(In this case, the only female case recorded, the urine was drawn off by catheter.) The patient had an extremely severe attack of fever followed by a relapse. The temperature was, however, coming down, when on Oct. 4th, 1899 (the fiftieth day of the disease), she experienced some pain and difficulty in micturition. The urine also was found to contain pus and typhoid bacilli were present in it in enormous numbers. On Oct. 6th the condition of the patient's urine was the same. She was put on urotropin—eight grains night and morning—and four days later, on Oct. 10th, on which day the temperature reached normal for good, the urine was found to be quite

natural in every way; cultures also proved it to be sterile. 72 grains of urotropin had in this case eliminated the micro-organisms.

It seemed probable from these cases that small quantities of urotropin—60 grains, for example—would be sufficient to free the urine permanently from typhoid bacilli. As a matter of fact, though this is sometimes the case it is not always true. If the urotropin be given only for a couple of days it may happen that after an apparent total disappearance from the urine the bacilli may return after the drug has been stopped and even become as numerous as before. The explanation doubtless is that a few isolated bacilli, having become lodged among the cells of the bladder wall, are thereby protected from the action of the drug and so escape destruction. As soon, however, as the urine ceases to contain formalin they begin to germinate again and the bacilluria returns. The following case is a good example of this class.

Case III. (Matthew Ward; Sir Dyce Duckworth).—The patient was a male, aged 24 years. He had a very severe attack of typhoid fever. The temperature reached normal for good on the twenty-seventh day (Nov. 17th, 1899) and did not rise again. The urine was examined on the eighteenth day (Nov. 8th) and was found to be turbid from the presence of myriads of typhoid bacilli. It was acid and had a faint cloud of albumin. On the same day the patient was put on urotropin, 10 grains ter die. The drug was continued until 60 grains had been given and was then stopped. The urine was examined after 20 grains of the drug had been taken and the most marked change was noticed in it (Fig. 6). Instead of being turbid from bacilli it was now quite clear and cultures (three drops of urine) showed no growth. Similar results were obtained from the urine after 40 and 60 grains had been taken. It seemed, therefore, that the patient was cured. This, however, was not so, for a week later, though the urine was clear, acid, and contained no albumin, cultures revealed the presence of many typhoid bacilli. Three days later, on the 20th, the condition was worse, the urine was now turbid with bacilli and contained pus. The upper layers of the urine after the pus had settled showed no albumin. On this day, therefore, the patient was again put on urotropin for two days, the drug being stopped after 60 grains had been administered. The result is instructive. After 20 grains had been taken the urine had again changed most marvellously. Instead of being turbid it was clear and contained no albumin or pus. Under the microscope, however, a few typhoid bacilli were seen and culture revealed the presence of many. After 30 grains cultures from three drops of the urine showed only 30 colonies of typhoid bacilli, after 40 grains only six colonies, while after 60 grains (Nov. 23rd) one colony only was obtained. The bacilli evidently had not

been entirely eliminated and, as might have been expected, they at once returned when the urotropin was stopped (Nov. 23rd). Thus four days later (Nov. 27th) the urine was again turbid and typhoid bacilli were found; it contained a little pus but no albumin. Urotropin was again ordered in the same dose but for a longer period of time. It was given from Nov. 27th to Dec. 4th, 210 grains being given in all. This proved completely successful. After 20 grains the urine again became clear and cultures revealed no typhoid bacilli. So also after 110 grains had been given. On Dec. 4th the urotropin was stopped, but the urine, though examined on Dec. 6th and 16th, never showed any return of the bacilluria. The case is of interest, then, as showing that sometimes the drug must be given for longer periods in order to effect a cure, and accordingly in the following case this was done.

Case IV. (Luke Ward; Dr. Gee).—The patient was a male, aged 36 years. He had an attack of medium severity, though the fever was prolonged, the temperature reaching normal only on the fifty-third day. The urine was examined bacteriologically three times during the attack, but it was always natural; typhoid bacilli were never present. Five days after defervescence, however (Nov. 24th, 1899), the urine was found to be turbid with typhoid bacilli and to show a deposit of pus. There was no pain or frequency of micturition; there was a cloud of albumin. On the following day (the 25th), the condition of the urine being the same, the patient was put on urotropin, 10 grains ter die. It was given for three days (Nov. 25th to 28th) and then stopped, 90 grains being given in all. After 20 grains had been taken the urine again showed the same marvellous change observed in other cases. Instead of being turbid with bacilli not a single bacillus could be seen under the microscope, though 24 colonies grew on a tube inoculated with three drops of urine. After 50 grains the urine was sterile and again after 80 grains (Nov. 28th). On this day (the 28th) the urotropin was stopped, but the urine, though tested on Dec. 1st, 6th, and 12th, never showed any return of the bacilli or pus; the cure was complete.

The three following cases are very similar. They all show the total disappearance of the bacilli after 30 grains of the drug, but to make sure of its permanence the administration was continued for a few days longer.

Case V. (Elizabeth Ward; Sir T. Lauder Brunton).—The patient was a male, aged six years. He had a severe attack of fever. The temperature reached normal for good on the thirtieth day (August 19th, 1899). Nothing abnormal had up to that time been noticed with regard to the urine. On the following day, however (the 20th), hæmaturia suddenly occurred. On the 22nd the hæmaturia was still present. Under the microscope, in addition to red corpuscles, pus

cells and many bacilli were seen, which latter proved on cultivation to be typhoid bacilli. The hæmaturia then ceased, but the bacilluria continuing the patient was put on urotropin, 10 grains three times a day, for four days (August 25th to the 29th), 120 grains being given in all. On the following day (the 26th) after 30 grains of the drug had been given the bacilli were found to have entirely disappeared. None could be seen under the microscope and none demonstrated by culture (Fig. 5). The same result was obtained on the 28th after 70 grains of the drug had been given. On the 29th the urotropin was stopped (120 grains having been given in all) and two days later (the 31st) cultures still showed the absence of typhoid bacilli.

Case VI. (Mark Ward ; Dr. Church).—The patient was a male, aged 20 years. He had a very severe attack followed by a relapse. The temperature reached normal for good on the fifty-first day. On Sept. 9th (the forty-fourth day, or fourth day of the relapse) the urine was natural in every way. It was clear, acid, and contained no albumin ; cultures showed the absence of typhoid bacilli. On Sept. 11th a marked change occurred. The urine was now turbid and contained innumerable typhoid bacilli ; it was acid and showed a very faint cloud of albumin. Five days later, on the 16th, a similar result was obtained. On this day the temperature reached normal for good. The patient was put on urotropin, 10 grains three times a day. On the following day, the 17th, after 30 grains of the drug the same marvellous change that has been noticed so often before was here again seen. The urine instead of being turbid with myriads of typhoid bacilli was now clear. No bacilli were seen under the microscope and none were revealed by culture. (Fig. 4.) After 60 grains also the same result was obtained. The urotropin was continued for four days (Sept. 16th to 20th), 120 grains being given in all. The urine was examined again on the 28th, but with a negative result, the cure being complete.

Case VII. (Colston Ward ; Dr. Hensley).—The patient was a man, aged 42 years. He suffered from an extremely severe attack of the fever, followed by a relapse. The temperature reached normal for good on the fifty-second day. The urine was examined on four occasions (the fourteenth, twenty-first, thirty-third, and forty-sixth days) during the attack. But though on the fourteenth day it contained one-fifth of albumin no typhoid bacilli were ever found. Nine days after defervescence, however (on Dec. 22nd, 1899), it was found to be turbid with typhoid bacilli. A week later (on the 29th) the bacilli were fewer in number but could still be seen under the microscope. The urine was acid and contained no albumin. The patient was now put on urotropin, 10 grains ter die, and on the following day, after 30 grains had been taken, the bacilli were found by culture (four drops) to have entirely disappeared. A similar result

was obtained on Jan. 2nd, 1900, after 160 grains had been administered. On the 4th the drug was stopped, 180 grains having been given in all. The urine was again examined on Jan. 8th but was still sterile.

Lastly, I may quote the following two cases in which after 50 and 60 grains respectively the bacilli were present, but in which they disappeared finally after a few more doses of the drug.

CASE VIII.—The patient was a male, aged 13 years. He was admitted late in the disease. The temperature reached normal on the twenty-seventh day. Two days later (Nov. 29th, 1899)—that is to say, when the temperature had been normal for two days—the urine was found to be bacilluric to the naked eye. It was acid and contained the faintest trace of albumin but no pus. The bacilli proved to be typhoid bacilli. On Dec. 1st and 2nd the condition remained unchanged. On the latter date urotropin, 10 grains three times a day, was ordered. On the following day (Dec. 3rd) a marked change had occurred after 20 grains only had been taken. The urine was found to be quite natural to the naked eye and to the microscope. It was clear, acid, and contained no albumin. No bacilli could be seen and culture (four drops) revealed none. A few, however, were still lurking in the bladder, for on Dec. 4th, the patient then having taken 50 grains of urotropin, one single colony did develop on the culture media. The drug was continued and the urine was again tested on Dec. 6th, when 140 grains had been administered. The urine now proved sterile. The urotropin was stopped, 140 grains having been given in all, but the urine tested by culture on subsequent occasions (on Dec. 9th and 16th) showed no return of the bacilli.

CASE IX.—The patient was a male, aged 31 years. The temperature reached normal on the thirty-first day for good. On Nov. 25th, 1899 (the twenty-third day), I first saw the urine. It was immediately seen by the naked eye to be turbid with micro-organisms which on culture proved to be typhoid bacilli. It was acid and contained no albumin, but showed a sediment of pus. There was no pain or frequency of micturition. On Nov. 29th the condition of the urine was the same; urotropin was prescribed in the same doses as before. On the following day (the 30th), after 30 grains had been taken, there was a marked improvement. The urine, however, still contained a little pus and under the microscope a few bacilli could be seen. Cultures showed many colonies. On Dec. 1st, after 60 grains had been taken, the urine was clear, contained no pus, and no bacilli could be seen; 21 colonies, however, developed on the cultures (four drops of urine). On Dec. 4th, 110 grains having been now given, the urine proved sterile. Two days later (Dec. 6th) the drug was stopped. In all 200 grains had been administered. Cultivations proved that the urine on this day contained no

typhoid bacilli and similar results were obtained on Dec. 9th and Dec. 16th. The bacilli in this case, then, disappeared after 110 grains of the drug had been given. To make certain, however, of a permanent cure 200 grains were given in all.

In conclusion, the following case may be briefly mentioned because it shows so clearly the long duration of the bacilluria if left untreated and the immediate and permanent effect of the drug in arresting it.

CASE X. (Colston Ward ; Dr. Hensley).—The patient was a man, aged 22 years. On admission, on the thirteenth day of his illness, he was found to be suffering from typhoid fever and nephritis. (The case is referred to in Lecture II.) The urine was turbid with typhoid bacilli, and this condition continued unaltered throughout his illness, being confirmed by bacteriological examinations made on the sixteenth, twenty-fifth, thirty-second, and thirty-fourth days. On the latter day (Jan. 24th, 1900) the temperature reached normal, the urine still containing myriads of typhoid bacilli. Urotropin, 10 grains three times a day, was ordered and was given from Jan. 24th to 31st, 210 grains being taken in all. On Jan. 25th, after 20 grains had been taken, colonies of typhoid bacilli still appeared in the culture tubes. But on the 26th, 27th, 29th, and 31st the urine was sterile. The drug was now stopped, but the cure had been permanent, for further bacteriological examinations made on Feb. 3rd, 5th, 9th, 14th, 19th, 26th, and March 7th showed no return of the micro-organisms.

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